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EFFECT OF MAGNESIUM SULFATE ON RENAL DYNAMICS IN ACUTE GLOMERULONEPHRITIS IN CHILDREN

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MAGNESIUM sulfate has been used extensively in the therapy of acute glomerulonephritis in children since its introduction by Blackfan[1] in 1925. The few studies[2,3] that have sought to elucidate the mode of action of the drug in this condition have shown that the magnesium ion is specifically responsible for the beneficial effects on the hypertension and encephalopathy. The mechanism is probably a direct vasodilation of the arterioles rather than a general body dehydration as first suggested.[1] Studies have not been reported of the effect of Mg on the function of the affected kidneys. In addition, little is known concerning renal dynamics in the early hypertensive phase of acute nephritis in children when Mg exerts its most dramatic therapeutic action.

The authors' approach to the problem was first to examine the effect of intravenous $MgSO_4$ on the renal function of normal dogs and then to make similar studies in normal and nephritic children. It was found that raising the level of plasma Mg in normal anaesthetized dogs failed to affect significantly either the glomerular filtration rate (GFR) or the effective renal plasma flow (RPF).[4] Since the blood pressure fell as the serum magnesium level rose, the afferent renal arterioles must have dilated to maintain intraglomerular pressure and therefore an unchanging RPF and GFR. This effect may have been due to a direct action of $MgSO_4$ on the renal arterioles or to the autonomous renal arteriolar changes described by Selkurt[5] which serve to maintain filtration rate and blood flow during changes in systemic arterial blood pressure.

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The next phase in these studies was to determine the effect of $MgSO_4$ on the renal dynamics of normal children and of those in the hypertensive and convalescent phases of acute nephritis. The results of these studies are the subject of this communication.

METHODS

Inulin and sodium para-aminohippurate clearances were used as indicators of GFR and of effective RPF, respectively. Plasma levels of these substances were established by priming doses intravenously and maintained with intravenous sustaining solutions. Plasma levels of para-aminohippurate were never greater than 3 mg./100 cc. and usually were below 2.0 mg./100 cc. Urine was collected by an indwelling catheter and complete bladder emptying was ensured by washing with 3 portions of distilled water. After an equilibration time of 30 to 40 min., 3 successive urine collection periods of 15 to 25 min. each were obtained. If the effect of $MgSO_4$ was to be determined, an intravenous infusion of drug was started at this time. Urine and plasma collections for renal function studies were continued. The desired level of plasma Mg was usually reached during the first collection period after the start of magnesium sulfate infusion, this period usually being 30 min. in duration. Thereafter, samples were collected for 2 additional periods of at least 15 min. each, the plasma magnesium level being maintained by intravenous infusion.

Cadmium sulfate filtrates of plasma and urine were analyzed in duplicate for inulin and para-aminohippurate by the methods of Goldring and Chasis[6] using an alcoholic diphenylamine reagent for inulin.[7] Magnesium was determined in serum by colorimetric phosphate analysis[8] of a magnesium ammonium phosphate precipitate.[9] All clearances were corrected to 1.73 sq.m. body surface.

RESULTS

Effect of Magnesium Sulfate on the Renal Dynamics of Normal Children:

As shown in tables 1 and 4 the average GFR was determined to be 148 cc./min. in four children. The average effective RPF was 709 cc./min. The average effective renal blood flow (RBF) was 1220 cc./min. and the average filtration fraction was 0.210. These values are comparable to those previously reported.[10–12] The values for filtration rate and fraction are somewhat higher than in other series, probably reflecting the fact that inulin gives approximately 10% higher values for clearance than does mannitol.[13,14]

No significant changes in GFR or effective RPF were noted in the four control children during the intravenous administration of $MgSo_4$ in amounts sufficient to raise the serum magnesium level to as high as 7.1 mg./100 cc. (table 4). As previously stated, similar results had been found in normal dogs.[4]

TABLE 1

EFFECTS OF MAGNESIUM SULFATE ON RENAL FUNCTION IN PATIENTS WITHOUT RENAL DISEASE

Case	Age (Yr.)	Sex	S. A.	Diagnosis	B. P. (mm.)	Therapy	Serum Mg. mg./100 cc.	GFR cc./min.	ERPF cc./min.	FF %	Urine Flow cc./min.	H'crit
1. C. T.	9	M	1.08	Healed Osteo	106/72	None	1.4	146	725	0.20	8.8	42.3
					90/71	$MgSO_4$	5.7	138	645	0.22	5.0	38.0
2. J. W.	7	M	0.91	Old Osteo	122/72	None	1.9	163	749	0.22	6.6	40.0
					110/45	$MgSO_4$	4.6	148	716	0.21	3.6	40.0
3. J. M.	8	F	0.98	Skin Blasto-mycosis	100/70	None	2.0	155	815	0.19	5.6	45.4
					100/80	$MgSO_4$	5.6	142	793	0.18	4.0	45.7
4. L. N.	9	F	0.90	Healed Abscess	94/40	None	2.0	127	548	0.23	1.3	38.3
					96/40	$MgSO_4$	7.1	122	571	0.21	3.6	38.2

TABLE 2

EFFECTS OF MAGNESIUM SULFATE ON RENAL FUNCTION IN ACUTE GLOMERULONEPHRITIS

Case	Age (Yr.)	Sex	S.A.	Day of Illness	B. P. (mm.)	Therapy	Serum Mg. mg./cc.	GFR cc./min.	ERPF cc./min.	FF	Urine Flow cc./min.	H'crit
1. J. D.	7	F	0.9	10	160/95	None		104	476	0.22	1.2	
			0.9	17	100/70	None		92	514	0.18	4.7	
2. D. G.	5	M	0.72	4	125/85	None		78	393	0.198	1.6	37.0
					125/85	$MgSO_4$	3.00	86	407	0.215	3.4	37.0
			0.67	16	100/70	None		131	701	0.194	3.8	39.0
3. G. L.	8	F	0.96	6	150/105	None	1.79	112			5.4	36.0
					118/75	$MgSO_4$	4.67	108	+17%	−18%	5.1	36.0
			0.96	15	100/60	None		112	702	0.16	6.5	38.0
4. H. H.	5	M	0.88	7	155/115	None	1.94	186	688	0.27	1.87	26.0
					122/98	$MgSO_4$	2.82	171	749	0.23	5.8	26.0
			0.84	13	100/65	None		142	877	0.16		26.0
5. C. G.	7	M	0.95	2	138/103	None	2.06	91	535	0.169	2.3	32.5
					110/78	$MgSO_4$	7.70	100	689	0.145	4.1	31.5
			0.93	13	92/62	None	2.02	107	642	0.167	4.0	33.0
					90/60	$MgSO_4$	5.60	101	920	0.110	5.0	33.0
6. W. O.	4	M	0.71	2	130/84	None	2.50	34.4	348	0.099	0.2	32.0
					110/77	$MgSO_4$	7.40	53.4	611	0.088	0.7	32.0
			0.65	22	107/60	None	2.26	134	750	0.180	1.5	34.5
					115/72	$MgSO_4$	7.80	152	1085	0.140	1.8	34.5
7. E. B.	11	F	1.31	6	148/116	None	2.62	65	417	0.156	1.6	36.0
					140/82	$MgSO_4$	5.50	67	535	0.126	1.9	36.0
			1.22	22	104/64	None	1.90	114	565	0.200	4.7	41.0
					105/72	$MgSO_4$	4.00	114	686	0.170	2.6	39.0
8. W. J.	5	F	0.79	8	128/86	None	2.3	68	348	0.196	0.94	35.5
					115/70	$MgSO_4$	6.0	82	515	0.160	2.46	35.5
			0.76	13	102/68	None	2.2	94	687	0.136	4.0	39.0
					110/55	$MgSO_4$	6.6	96	744	0.128	5.5	39.0
9. D. R.	10	M	1.08	8–17	138/90	None	2.46	38.6	314	0.123	0.73	31.5
					125/72	$MgSO_4$	6.70	39.7	336	0.118	1.18	30.7
			1.07	9 days later	130/90	None	2.50	43.0	328	0.131	1.2	32.7
					126/65	$MgSO_4$	7.70	65.0	510	0.128	2.9	33.1
10. R. H.	8	M	0.95	4	160/106	None	2.38	72.5	488	0.149	0.25	33.0
					130/90	$MgSO_4$	6.70	91.0	737	0.123	0.78	32.5
11. C. H.	37	M	1.62	9	140/80	None	2.13	95.0	623	0.152		46.5
					120/75	$MgSO_4$	5.40	113.0	774	0.147	5.9	43.9

TABLE 3

RENAL DYNAMICS IN ACUTE NEPHRITIS

	GFR	ERPF	ERBF	FF
Controls	148 (±16)*	709 (±114)	1220 (±247)	0.210 (±0.018)
Acute Nephritis				
Early Stage	82 (±45)	445 (±117)	655 (±157)	0.175 (±0.052)
Later Stage	108 (±30)	641 (±157)	1018 (±231)	0.168 (±0.024)

* Numbers in parentheses are standard deviations.

Renal Dynamics During Early Hypertensive Phase of Acute Nephritis and During Recovery Period One to Three Weeks Later (tables 2 and 3):

In nine children with acute nephritis in the early hypertensive phase, the average GFR was 82 cc./min., the average effective RPF was 445 cc./min., the average filtration fraction was 0.175, and the effective RBF was 655 cc./min. The mean GFR was significantly lower than the normal (by the t test, p was between 0.01 and 0.02). The mean effective RPF and RBF also were significantly lower than the normal (p less than 0.01), but the mean filtration fraction did not show significant change from the normal. One patient (H.H.) showed a renal function pattern which was markedly different from the others in the series because of the presence of a very high GFR and consequently of an elevated filtration fraction. This patient did not differ in clinical condition or course from other members of this series and the authors cannot account for this isolated finding. If this patient were omitted from the series, the average renal function values would be as follows: GFR 69 ± 24, effective RPF 415 ± 79, effective RBF 615 ± 120, and filtration fraction 0.164 ± 0.041. In general, the filtration rates and plasma flows were much reduced while the filtration fractions were more variable, being below 0.19 in five patients, 0.19 to 0.23 in three patients and high (0.27) in the previously mentioned child.

In those patients studied during convalescence, 1 to 3 weeks after the initial determinations, the average GFR had increased to 108 ± 30 cc./min. (plus 32%), the average effective RPF had increased to 641 ± 157 cc./min. (plus 43%) and the average effective RBF had increased to 1018 ± 231 (plus 56%). Meanwhile, the average filtration fraction had decreased from 0.175 to 0.168. In this series the mean effective RPF and RBF were significantly higher than during the early stage (p of less than 0.01), but no longer differed significantly from the normal means. The mean filtration fraction had dropped sufficiently in the later stage to differ significantly from the normal (p less than 0.02).

These results confirmed previous observations of a low filtration rate during the acute phase of nephritis.[10, 15–19] On the other hand, the present series demonstrated a more comparable reduction of the effective RPF so that the filtration fractions in some instances were normal rather than uniformly reduced. The difference may be in part caused by the fact that the studies in the present series usually were performed earlier in the disease than those previously reported, and were done only in children where the natural history of the disease is different from that in the adult. The significance and mechanism of the

reduction in RPF and RBF in the early phase of nephritis will be discussed later.

When the children were restudied 1 to 3 weeks later, the rates for both glomerular filtration and RPF were found to have increased markedly in the majority of patients. At this time, although the average filtration fraction showed little change from the earlier value, there was less variation in the series than previously and all fractions were 0.20 or below. The data indicated that very early in the course of acute nephritis, both filtration rate and RPF are markedly reduced. The relation between the extent of reduction in filtration rate to that in plasma flow was not identical in different patients so that the filtration fractions were quite variable and may be normal or increased. Although the higher filtration fractions may be determined by the same causes that operate in patients with cardiac failure, no manifestations of overt failure were detected in the children of the present series. Later during recovery from the acute process, the GFR was usually reduced to a greater extent, percentagewise, than was the RBF so that the filtration fractions were usually subnormal. This pattern of renal function during convalescence corresponds to that found in acute nephritis by most investigators, probably because the disease had been studied too late in its course to demonstrate the early variability in the filtration fractions.

Effect of Magnesium Sulfate on Renal Dynamics of Children with Acute Nephritis During the Hypertensive Phase and During Early Recovery One to Three Weeks Later (table 4):

To determine the effect of $MgSO_4$ on kidney function in patients with acute nephritis, a 2 or 3% solution of the hydrated salt in distilled water was administered intravenously after several control collection periods for clearance studies had been completed. When the 2% solution was given slowly in small quantities, no effect on renal function was

TABLE 4

EFFECT OF MAGNESIUM SULFATE ON RENAL DYNAMICS

	GFR	ERPF	ERBF	FF
Controls				
Before $MgSO_4$	148 (±16)*	709 (±114)	1220 (±241)	0.21 (±0.018)
During $MgSO_4$	137 (±11)	681 (±111)	1154 (±231)	0.21 (±0.017)
Hypertensive Acute Nephritis				
Before $MgSO_4$	59 (±20)	397 (±85)	596 (±129)	0.147 (±0.031)
During $MgSO_4$	71 (±21)	561 (±132)	839 (±194)	0.127 (±0.071)
Subsiding Acute Nephritis				
Before $MgSO_4$	112 (±16)	661 (±77)	1047 (±102)	0.171 (±0.026)
During $MgSO_4$	116 (±25)	859 (±80)	1340 (±233)	137 (±0.025)

* Numbers in parentheses refer to standard deviations.

observed. The rate of administration of the salt was increased in different patients until plasma magnesium concentrations greater than 5 mg./100 cc. were obtained. The routine eventually adopted consisted of the intravenous administration of a 3% solution at an initial rate of 4 cc./min. When the blood pressure began to fall or cutaneous vasodilation with an uncomfortable sense of warmth appeared, the rate was slowed to 1 to 2 cc./min. and continued until three additional collection periods were obtained. The total amount of $MgSO_4$ given was 1.2 to 5.3 gm. depending upon the size and condition of the child.

When $MgSO_4$ was administered in this manner to seven patients in the hypertensive phase of acute nephritis, an increase in GFR of from 3 to 55% (average of 24%) was observed over the control period. The RPF increased 7 to 76% with an average increase of 42%. Analysis by the paired data technic showed that the increases in both filtration rate and plasma flow were highly significant ($p < 0.01$). The greater increase, percentagewise, in effective RPF than in GFR resulted in a highly significant fall in the filtration fraction.

The lowest figures for rises in GFR and RPF were obtained in Patient D.R.

D.R. (C-74014), a 10 yr. old boy, developed edema insidiously 14 days prior to admission and without any known precipitating illness. He was noted to have dark red urine, frequency and nocturia. Renal function studies were done 3 days after admission when blood pressure was 138/90 mm.Hg (Fig. 1). Three control periods showed an average GFR of 39, effective RPF of 314, and filtration

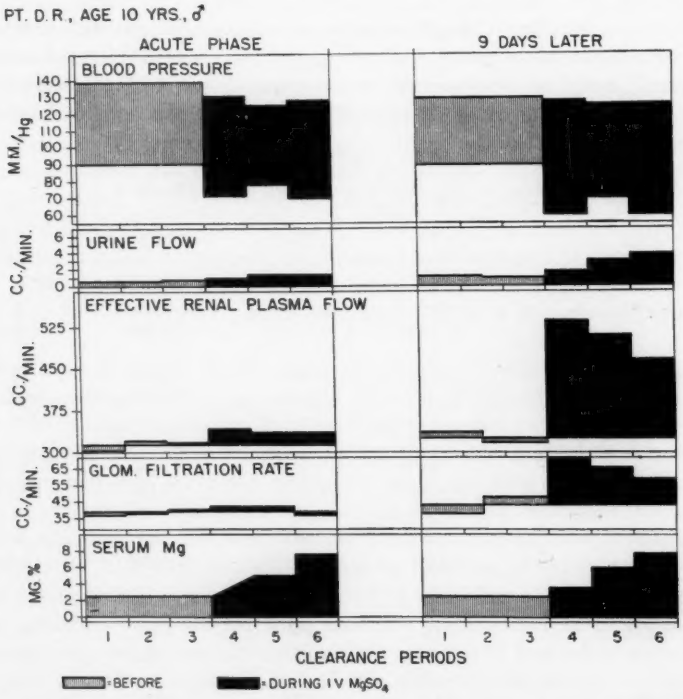

FIG. 1. Renal function before and during magnesium sulfate administration in Patient D.R. In left half of figure are results obtained during early acute phase of nephritis. Results obtained 9 days later are shown in right half of figure.

fraction of 0.12. Despite administration of 129 cc. 3% magnesium sulfate solution in 65 min. (a total dose of 127 mg./kg. body weight), there was no appreciable change in GFR or RPF. Blood pressure, however, fell to 125/72 mm.Hg while serum magnesium level rose from 2.5 to 6.7 mg./100 cc.

During the next 9 days, he was placed on a regime of bed rest, low salt diet, penicillin and unlimited fluids. He was asymptomatic and lost 1 kg. in weight. Blood pressure stabilized at 130/90 mm.Hg. Renal function studies then showed low values during control periods (GFR 43, effective RPF 328, filtration fraction 0.13) as had been obtained on previous examination 9 days before. He was given a total of 121 cc. of 3% magnesium sulfate solution intravenously during 3 collection periods totalling 58 min. (total dose of 125 mg./kg. body weight). Effective RPF rose to 551 during first magnesium sulfate period and then fell somewhat to average 510 cc./min. during the 3 periods, a rise of 55% over the control periods. The GFR rose to an average of 65 cc./min., a rise of 51%. Blood pressure fell to 126/65 mm.Hg and serum Mg rose to 7.7 mg./100 cc. A pronounced diuretic effect was also seen.

This patient differed from the others in the group in having an insidious onset and a more persistent hypertension. Magnesium sulfate had no effect on renal function at the first trial. At this time, diagnosis of an acute exacerbation of a chronic nephritis was considered. However, 9 days later, Mg showed the expected marked effect on kidney clearances. It may be that the kidneys were only relatively unresponsive to the effects of Mg on the first try and that higher levels would have caused the desired result. The actual doses used in this case were smaller than is now considered optimal. However, this case was also markedly different from the others in that there was no improvement in clearances over the 9 day period between studies. The authors were particularly interested in his follow-up to ascertain whether this peculiar behavior might be indicative of a chronic progressive process. However, the disease process gradually subsided and one year later, the Addis count was found to be within normal limits.

In an additional four cases, the determination of the effect of Mg was repeated 5 to 20 days later. At this time, the patients were markedly improved and their blood pressure levels were within normal limits. The average change in GFR on the administration of $MgSO_4$ was plus 2.5% (−6 to +13%), but the effective RPF still increased appreciably (range from 8 to 45% with an average increase of 30%). In two cases (C.G. and W.O.) the effective RBF may have risen to supranormal levels during the magnesium therapy. This was never observed in normal children or animals.

The protocols of three patients are presented to illustrate the technic employed and the results usually obtained.

W.O. (No. C-10009), a 4 yr. old boy, developed edema, oliguria and smoky urine 14 days after onset of impetigo. He was studied 2 days later when blood pressure was 130/84 mm.Hg. As seen in figure 2, GFR was 34 cc./min. and effective RPF was 348 cc./min. (corrected to 1.73 sq.m. body surface) during the 3 control periods. An intravenous infusion of 3% hydrated magnesium sulfate solution was then started at a rate of 2 to 3 cc./min. but was slowed shortly thereafter to 1 to 2 cc./min. so that 51 cc. was administered during the first period of 30 min. Serum Mg rose from 2.5 mg./100 cc. to 4.6 mg./100 cc. by the mid-point of this period. Blood pressure fell to and was easily maintained at 108/78 mm.Hg. At the same time, GFR rose to 50 cc. and effective RPF to 660 cc./min. Magnesium sulfate solution was continued at 1 to 2 cc./min. for additional periods of 26 and 18 min. Total amount given was 117 cc. in 74 min. or 3.51 gm. of the salt, i.e., 195 mg./kg. body weight. Serum magnesium concentration eventually rose to 7.4 mg./100 cc. Despite further rise in serum Mg and maintenance of blood pressure at the same lowered level, RPF decreased somewhat during last 2 periods. This effect was seen not infrequently and resembled the course of mild cutaneous vasodilation which was more pronounced during the early and rapid rise in plasma Mg than later when a more steady level was achieved.

Following these studies, patient was kept at bed rest on a salt-poor diet and was treated only with penicillin for his pyoderma. He lost 2 kg. in weight and appeared well though urine still showed albuminuria and slight hematuria. After an interval of 19 days, renal studies were repeated. GFR had risen to 134 cc./min. while effective RPF had risen to 750. A total of 102 cc. of 3% magnesium sulfate solution was then administered intravenously in 64 min., causing a rise in serum Mg to 7.8

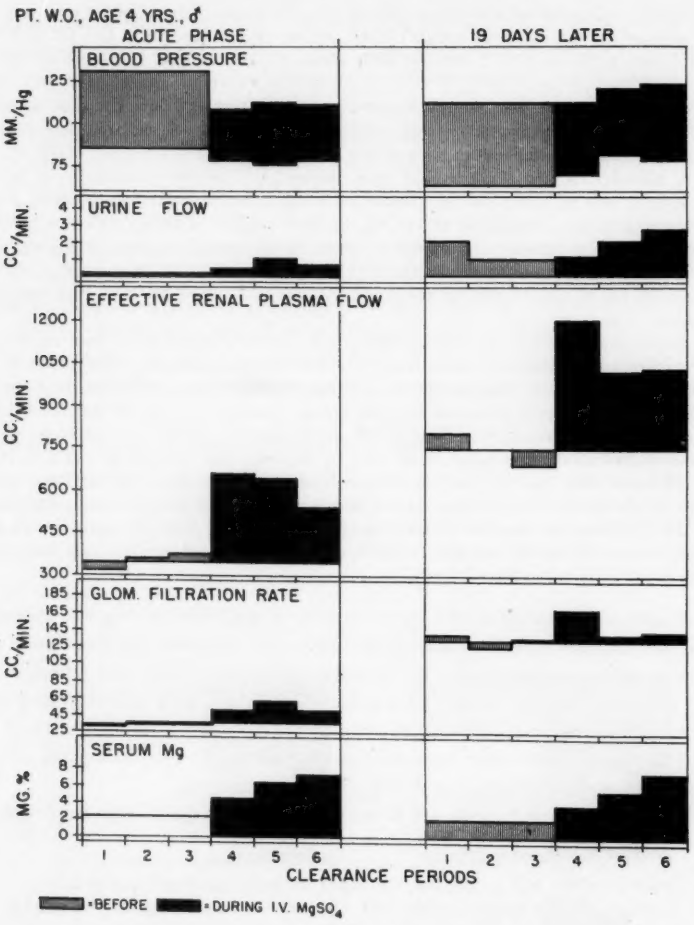

FIG. 2. Renal function in Patient W.O. For explanation, see Fig. 1.

mg./100 cc. but not producing any fall in his now normal blood pressure. However, RPF rose to 1210 cc./min. and then fell to 1025 despite a further rise in serum magnesium level. GFR remained essentially unchanged during administration of $MgSO_4$.

No untoward reactions were observed during or after the studies. He remained well in appearance and Addis count returned to normal within 6 mo.

R.H. (No. C-76916), an 8 yr. old boy, had a sore throat which cleared in 3 days. Eleven days after onset, he developed facial edema, oliguria and smoky urine which progressed in intensity for 2 to 3 days until he was admitted to the hospital. Five siblings and the father in this family had acute nephritis at the same time. Beta hemolytic streptococcus, Group A type 12,* was cultured from every member of the family, including the mother and an 18 mo. old infant who did not develop nephritis.

On the day after admission, 4 days after onset of nephritis, GFR was found to be 73 cc./min. and effective RPF to be 488 cc./min. (Fig. 3). Blood pressure during this time was 160/105 mm.Hg.

* The authors are indebted to Dr. John H. Dingle, Western Reserve University School of Medicine, Cleveland, for identifying these organisms.

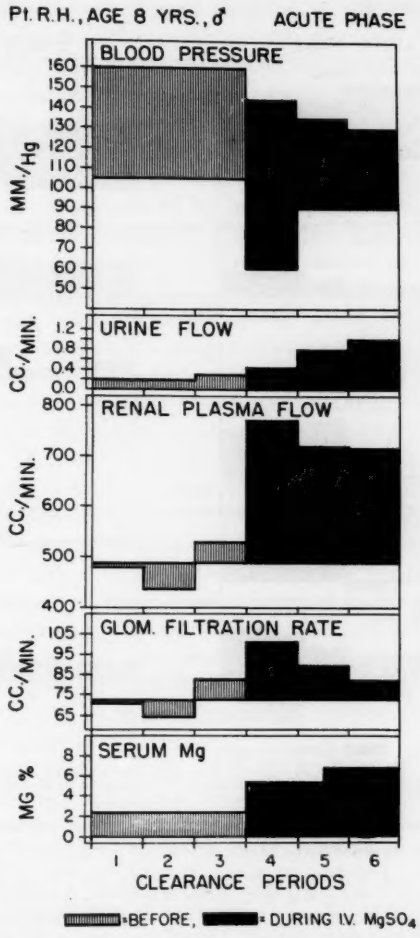

FIG. 3. Renal function before and during magnesium sulfate administration in Patient R.H. during early hypertensive phase of nephritis.

Intravenous administration of 3% magnesium sulfate solution was started and 52 cc. given during the first period of 27 min. 43 cc. and 37 cc. were given during 2nd and 3rd periods which lasted 18 min. each. A total of 132 cc. was given in 63 min., a dose of 147 mg./kg. body weight. Blood pressure fell to 144/60 mm.Hg and then to 130/90 mm. while the serum Mg rose from 2.4 to 5.3 and 6.7 mg./100 cc. GFR increased to an average of 91 cc./min. during magnesium administration. Effective RPF rose to 737 cc., an increase of 51%, while urine flow increased from 0.3 to 0.4, 0.8, and 1.1 cc./min. during the 3 magnesium periods. Because of the greater rise in effective RPF than in GFR during magnesium administration, filtration fraction dropped from 0.15 to 0.12.

No further clearance studies were done. Patient recovered uneventfully and Addis count returned to normal in 4 mo.

W.J. (C-68141), a 5 yr. old girl, developed periorbital edema 7 days after onset of impetigo. Five days later she showed ankle edema and when examined after another 2 days had a blood pressure of 158/110 mm.Hg, edema, moderate albuminuria and slight hematuria. The next day renal studies were performed (Fig. 4). During 3 control periods, blood pressure was 128/86 mm.Hg.

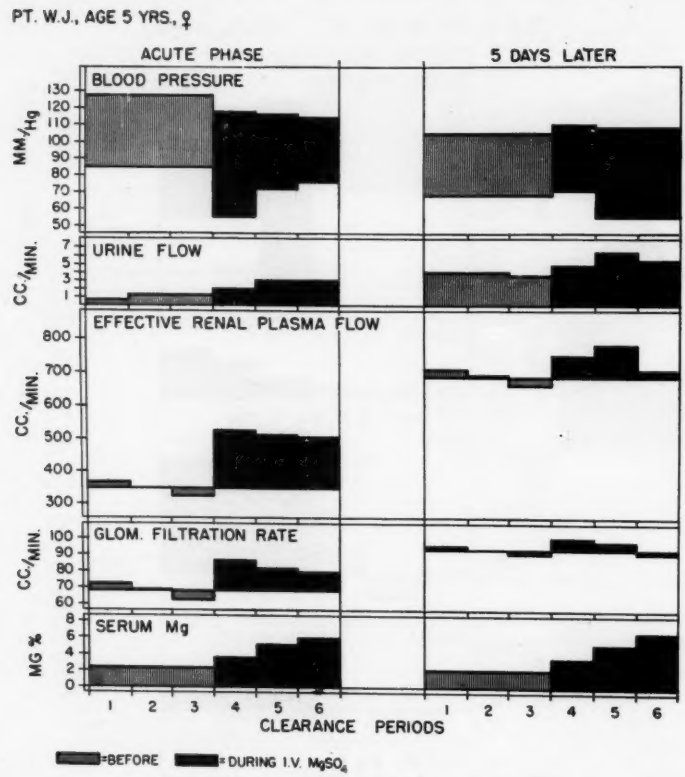

FIG. 4. Renal function in Patient W.J. Legend as in Fig. 1.

GFR was 68 cc./min. and effective RPF was 348 cc./min. Three per cent hydrated magnesium sulfate solution was then started intravenously. 54 cc. were given during the 27 min. of 1st period and 26 cc. during 2nd and 3rd periods of 17 min. each. Total dose was 106 cc. in 60 min., 160 mg. of the salt/kg. body weight. During this time, serum magnesium concentration rose from 2.3 to 6.0 mg./100 cc. and blood pressure fell to 115/75—40 mm.Hg. GFR rose to an average of 82 cc./min. while effective RPF increased to 515 cc./min.

On a regime of bed rest, low salt diet, penicillin, fluids *ad libitum*, patient lost 3 kg. body weight in 5 days. When restudied at that time, GFR had risen to 94 cc./min. and effective RPF to 687 cc./min. She was then given 103 cc. magnesium sulfate solution during 3 collection periods totalling 68 min. Serum Mg rose to 6.6 mg./100 cc. but blood pressure, GFR and effective RPF did not show appreciable changes.

Patient remained in good health and Addis count returned to normal in 6 mo.

DISCUSSION

It has been shown that the intravenous administration of $MgSO_4$ usually causes an increase in filtration rate and effective RPF during the early hypertensive phase of acute nephritis in childhood. These changes occur in spite of the fall in blood pressure which is produced by the drug. On the other hand, administration of $MgSO_4$ during convalescence from acute nephritis usually fails to alter filtration rate although it still may produce an increase in effective RPF.

The mechanism whereby Mg increases the filtration rate may involve an increase in

filtration pressure, the opening of additional glomeruli, an alteration in the permeability of the glomerulus or a change in the protein or water content of the plasma. Since the drug does not appreciably affect the plasma protein or water concentration[20] and does not have a specific effect on general capillary permeability, the increase in filtration rate must be secondary to a rise in perfusion pressure and/or the opening of glomeruli which had previously not been functioning. The rise in glomerular pressure takes place despite the concomitant fall in systemic arterial pressure.

The increase in effective RPF caused by Mg in acute nephritis may be due to an alteration in renal vasculature so that resistance to effective blood flow is decreased to a greater extent than mean systemic blood pressure. It is also possible that the rise in effective RPF, as measured by para-aminohippurate clearance, is not real and is based upon an improvement in hippurate extraction caused by Mg. If Mg can cause an increase in effective RBF to supranormal levels as it seems to have done in Case W.O., an increase in para-aminohippurate extraction cannot be involved as extraction is practically complete in normal individuals. The extraction ratio was directly determined during administration of $MgSO_4$ in one adult (C.H.) with acute hypertensive nephritis.* Although Mg caused an increase of 24% in effective RPF and of 19% in GFR in this patient, there was no change in the extraction ratio of para-aminohippurate (0.90 before and 0.88 during magnesium sulfate administration).

The failure of Mg to increase the extraction ratio eliminates from consideration both an effect on tubular efficiency as well as a closure of shunts through which blood might by-pass functional tubular tissue. Magnesium sulfate must therefore cause a real increase in RBF in acute nephritis with hypertension. As a corollary, the low effective RBF found in the present series must be in part due to a renal vasospasm which is relieved by Mg. The renal vessels apparently share in the general vasoconstriction observed in this disease. The simultaneous increase in GFR and in effective RPF indicates that the spasm is present to some extent in the preglomerular vessels.

These conclusions are contrary to the results of Bradley and his co-workers[19] who found that although the effective RBF was low in acute nephritis, the true blood flow was relatively normal. However, they measured the para-aminohippurate extraction ratio in only one child during the acute hypertensive phase of the disease. In this case, the true RBF was at the lower limits of normal. In the cases reported here, for the reasons given above, it is unlikely that poor tubular extraction alone can account for the low effective RPF. However, it will be noted that $MgSO_4$ usually does not increase the estimated plasma flow to normal during the acute hypertensive phase. It is possible that Mg increases the true blood flow to normal but the effective RBF, as measured by para-aminohippurate clearance, remains low in some patients due to a low extraction ratio.

The demonstration of a renal vasospasm in acute nephritis recalls the opinions of Volhard[21] who postulated that there was a disturbed circulation through the glomeruli and that this disturbance was caused by vasoconstriction rather than by anatomic alterations such as plugging or proliferative processes. It explains the observations of pathologists who have noted that "one sometimes gets the impression that the glomerular lesion is the result of simple ischemia and is comparable to a genuine infarct."[22] These observations and the present studies do not answer Volhard's question as to whether the renal vasoconstriction is but a part of the general ischemia or whether the peripheral

* The authors are indebted to Dr. John B. Hickam of the Department of Medicine, Duke University School of Medicine, for the renal-vein catheterization of this patient.

vasoconstriction is secondary to the renal process. However, general vasoconstriction with hypertension may be present with minimal urinary signs[20,23] and renal vasospasm may be present after the general vasoconstriction has largely subsided. Such observations cast some doubt on the concept of acute nephritis as a primary kidney disease.

The presence of renal vasospasm when the general blood pressure is not much elevated and its persistence for some time after the blood pressure has become normal has broad therapeutic implications. It may be possible to protect the kidney from the effects of vasospasm with $MgSO_4$. Ellis has suggested that a precapillary vasospasm may be the immediate cause of glomerular haemorrhage in acute nephritis.[24] Should $MgSO_4$ be administered to all cases of acute nephritis regardless as to whether there is sufficient generalized vasospasm to produce clinical hypertension?

A number of clinical observations were made while treating the patients in this series and others in whom complete function studies could not be made because of either age, poor cooperation or extreme severity of symptoms.

The intravenous administration of $MgSO_4$ was usually accompanied by a diuresis of appreciable magnitude (table 2 and Figs. 1-4). This diuresis may not be solely due to an osmotic effect but is probably also the result of the increased filtration rate and the relief of renal vasospasm. It was frequently maintained after the infusion had been discontinued and the drug was being given intramuscularly. Such a regime to produce diuresis would appear to rest on a sounder physiologic basis than the thirst and *wasserstoss* therapy of Volhard.[21]

If the action of $MgSO_4$ is primarily on the vascular spasm of acute nephritis and the symptoms of hypertensive encephalopathy are a result of this spasm, then one of the first actions of the drug must be on the cerebral vessels. The authors have repeatedly noted that cerebral symptoms such as stupor, convulsions or headaches were relieved during the administration of $MgSO_4$ before there was an appreciable drop in blood pressure. It was also possible to cause improvement in the symptoms of hypertensive encephalopathy by intravenous administration of $MgSO_4$ without producing a drop in blood pressure. Further, in those cases where insufficient Mg had been given, either intravenously or intramuscularly, to lower the blood pressure for a prolonged period, the symptoms of hypertensive encephalopathy did not tend to return even though the blood pressure may have returned to the original level. Apparently, the effect on the cerebral vessels is also more prolonged than the effect generally in causing a fall in blood pressure. These observations point to the need for studying the cerebral circulation in acute nephritis and the effect of $MgSO_4$ on the cerebral vessels. Incidentally the retinal vessels seemed narrow in many patients when cerebral symptoms were prominent. These vessels quickly dilated to normal caliber during the infusion of $MgSO_4$.

It was noted early in these studies that larger doses of $MgSO_4$ than generally advised had to be given intravenously in order to lower the blood pressure. The minimal effective serum magnesium concentration was found to be approximately 5 mg./100 cc. This figure agrees well with that found by Winkler et al.[25] in adults and by Butler and Reyersbach[26] in children with acute nephritis. In some children, the serum concentration had to be increased above this level, to 7 or 8 mg./100 cc. Once a satisfactory serum magnesium concentration had been achieved in the individual patient, the infusion rate could be adjusted so that a slight decrease would cause the blood pressure to rise and a slight increase would cause a further fall in pressure. Apparently, a critical plasma concentration is reached and a minimal rate of infusion must be kept in order to maintain this level. The total dose suggested by these studies is 150 to 200 mg. hydrated $MgSO_4$/

kg. body weight given as a 3% solution (5 to 7 cc./kg.) in the course of one hour. One half of this dose can usually be given as previously described in the first 15 to 20 minutes depending upon the blood pressure and clinical response.

Save for an occasional skin flushing and complaint of feeling warm, no toxic symptoms were observed when the drug was given in this fashion. Although Ca-gluconate was kept immediately available (in a sterile syringe) as an antidote, it was not needed at any time. Signs of nervous system depression, such as slow respirations, did not appear. It is therefore unlikely that the therapeutic effectiveness of the drug in controlling convulsions can be ascribed to the depressant effects which are noted at much elevated plasma magnesium concentrations.

The urinary excretion of Mg during the time of the infusion of the drug was determined in the four controls and nine times in the patients. Calculations of the volume of distribution of the retained Mg showed that the Mg was probably confined to the extracellular space during this period of approximately one hour.* Since the plasma concentrations did not rise excessively during the infusions and since the volume of distribution had risen to approximate that of the extracellular fluid within one hour, equilibration of Mg between plasma and extracellular fluid must be quite rapid in the nephritic patient as it is in the normal.[27] If equilibration is allowed to take place by injecting slowly as suggested, the dose which the authors advise (150 to 200 mg. hydrated salt/kg.) should not cause severely toxic plasma magnesium levels even if no urinary excretion occurs. Urinary loss of Mg will naturally diminish the rise in plasma Mg. In the very early hypertensive phases of acute nephritis, it was found that approximately 5% of the administered Mg was excreted during the course of the infusion. Later, during recovery, approximately 10% was so excreted. These figures contrast with the average of 23% urinary excretion in the four normal children. The presence of an increased extracellular phase in edematous patients will also tend to decrease the extent to which the plasma Mg is elevated by the infusion. To some extent, the two factors of excretion and distribution balance each other during acute nephritis. Early in the disease, the edema is usually more marked (tending to diminish the rise of plasma magnesium concentration) but the extent of urinary excretion is usually small (tending to cause larger rises in plasma Mg). Later during recovery the converse is more frequently seen. It is perhaps for this reason that the dose of Mg, which has been determined solely from the clinical effects, tended to be quite similar for most patients.

The amount of $MgSO_4$ which must be given intramuscularly to maintain the level produced by the intravenous route is now being investigated. It will naturally depend upon the extent of loss of Mg from the extracellular fluids into the cells[27] and through channels of excretion such as urine, sweat and stools. Since these factors have not yet been determined for the child with acute nephritis, this amount to be administered must be determined at present solely on clinical grounds or after the analysis of the plasma for magnesium content.

It is interesting to compare the effects on the kidneys of several agents which have been used for the therapy of hypertension in acute nephritis. 2 benzyl-4,5 imidazoline (priscoline®) has been found to induce a neurogenically mediated afferent arteriolar vasoconstriction even in normal humans.[28] The result is a marked fall in RPF and in

* The extracellular space was assumed to be 25% of the patient's weight after loss of edema fluid. The difference between the patient's weight during obvious edema and his weight after subsidence of edema was added to the above figure to obtain the approximate extracellular space during the edematous phase of the disease.

filtration rate. Since these changes might have an adverse effect on an already damaged kidney, the practice of using this drug in nephritis does not appear logical.[29] In contrast, 1 hydrazino-phthalazine (aprescoline®) causes an increase in RBF in the normal[30] and has recently been shown to lower the blood pressure in acute nephritis.[31] However this drug can severely depress renal function in nephritis, especially the filtration rate but also occasionally the RBF.[31] The action of $MgSO_4$, on the other hand, is unique. It does not alter renal function in normal individuals. Long experience by many clinicians has shown it to be almost universally effective in controlling hypertensive encephalopathy and in lowering blood pressure in acute nephritis. In addition, the studies herein reported demonstrate that it has a beneficial effiect on renal function in acute nephritis—the extent of which usually is greatest in the earliest stages of the disease when it is probably most needed.

SUMMARY

Renal function was determined in children before and during the intravenous administration of $MgSO_4$. These studies were performed on normal children and on children with acute nephritis; in the latter, both during the acute hypertensive phase of the disease and during convalescence 1 to 3 weeks later. Glomerular filtration rates and effective RPF were markedly subnormal during the hypertensive stage and increased toward normal during convalescence. The intravenous administration of $MgSO_4$ caused marked rises in GFR and in effective RPF when given during the hypertensive stage. Magnesium produced smaller rises in effective RPF but no changes in GFR when given during convalescence. Changes in renal function were not caused by Mg in normal children.

The implications of these findings are discussed with reference to the treatment and pathophysiology of acute nephritis. It is suggested that renal vasospasm is present in children with acute glomerulonephritis and that adequate therapy with $MgSO_4$ relaxes this vasospasm.

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SPANISH ABSTRACT

El Efecto del Sulfato de Magnesio en la Dinámica Renal de la Glomerulonefritis Aguda en los Niños

El sulfato de magnesia que se ha usado extensamente en el tratamiento de la glomerulonefritis aguda de los niños, no ha sido estudiado en su efecto sobre la función del riñón enfermo y poco se sabe sobre la dinámica renal en la fase hipertensiva temprana de la nefritis aguda infantil en la que el sulfato de magnesio ejerce su acción terapéutica mas dramática. Los estudios escasos hechos para dilucidar su modo de acción han mostrado que el ion magnesio es responsable específicamente de los efectos benéficos en la hipertensión y la encefalopatía de las glomerulonefritis aguda, probablemente por vasodilatación directa de las arteriolas.

Previamente los autores estudiaron el efecto del sulfato de magnesio intravenoso en la función renal de perros normales encontrando que la elevación del nivel plasmático del magnesio no afectaba significativamente ni la velocidad de filtración glomerular ni el flujo renal plasmático efectivo. Esto les permitió concluir que las arteriolas renales aferentes debían haberse dilatado para mantener la presion intraglomerular puesto que la presion arterial descendió a medida que el nivel del magnesio se elevaba. Este efecto pudo ser debido a acción directa del sulfato de magnesia en las arteriolas renales o a los cambios autónomos de las arteriolas renales, que sirven para mantener la filtración y flujo sanguíneo durante los cambios de la presión arterial sistémica.

En este artículo los autores reportan sus estudios sobre el efecto del sulfato de magnesio en la dinámica renal de niños normales y de aquellos con nefritis aguda, en los cuales determinaron la función renal en ambos grupos antes y durante la administración intravenosa de sulfato de magnesio.

En los nefríticos se escogió la fase hipertensiva y durante la convalescencia, de una a tres semanas mas tarde, para realizar las pruebas.

Los resultados muestran que la velocidad de filtración glomerular y el flujo plasmático renal efectivo eran francamente subnormales durante el período hipertensivo y que se elevaron a lo normal durante la convalescencia. Durante la fase hipertensiva la administración intravenosa de sulfato de magnesio produjo una elevación marcada en la velocidad de filtración glomerular y en el flujo plasmático renal efectivo. Cuando se administró durante la convalescencia el magnesio, produjo elevaciones mas pequeñas, en el flujo plasmático renal efectivo pero la velocidad de filtración glomerular no sufrió cambio alguno.

No se registró cambio alguno de la función renal en los niños normales, causados por el sulfato de magnesio.

La discusión del mecanismo por el cual el magnesio aumenta la velocidad de filtración les permitió eliminar el posible aumento de presión de filtración, la abertura adicional de glomérulos, una alteración de la permealidad de los glomérulos o un cambio en la proteína o contenido acuoso del plasma, como factores posibles de su acción, para aceptar que actúa en la nefritis aguda con hipertensión, determinando un aumento del flujo sanguíneo renal.

Como corolario, el bajo flujo plasmático renal efectivo que se encontró en ésta serie de enfermos debe ser en parte debido a un espasmo vascular renal que es mejorado por el magnesio. Aparentemente los vasos renales participan en la vasoconstricción general observada en esta enfermedad y el aumento simultáneo en la velocidad de filtración glomerular y en el flujo plasmático renal efectivo indican que el espasmo esta presente en cierto grado en los vasos preglomerulares.

Que la vasoconstricción renal sea solo parte de la izquemia general o la vasoconstricción periférica secundaria al proceso renal, no es posible contestarlo, sin embargo, puede existir la vasoconstricción general e hipertensión con signos urinarios mínimos y el espasmo renal puede estar presente después de que la vasoconstricción general ha descendido ampliamente, lo cual deja ciertas dudas acerca del concepto de la nefritis aguda como una enfermedad primaria del riñón.

La presencia del espasmo vascular renal, cuando la presión sanguínea no está muy elevada y su persistencia por algún tiempo después de que ésta última se ha hecho normal plantea la posibilidad de que el sulfato de magnesio proteja al riñón de los efectos del espasmo de las arteriolas renales ya que se ha sugerido que el vasospasmo precapilar puede ser causo inmediata de hemorragia glomerular, y que dicha sal deba ser administrada a todos los casos de nefritis aguda sin considerar la presencia de un espasmo vascular generalizado suficiente para producir hipertensión clínica.

Cierto número de observaciones clínicas hechas por los autores durante el tratamiento de los enfermos de esta serie y de otros incompletamente estudiados, hablan a favor de dicha posibilidad terapéutica del magnesio. Efectivamente, las siguientes observaciones la respaldan: en general el uso del magnesio se acompañó de diuresis de magnitud apreciable que frecuentemente se mantuvo después de suspender la administración intravenosa del sulfato y cuando se estaba dando intramuscularmente; la apreciación repetida de que los síntomas cerebrales, como el estupor, las convulsiones y las cefaleas mejoraran antes de que hubiera una caída apreciable de la presión sanguínea, o sin que se presentara en lo absoluto, lo que sostiene el concepto de que la encefalopatía hipertensiva es el resultado del espasmo vascular, y mas aún que los síntomas encefálicos no tiendan a volver aunque la presión sanguínea haya subido de nuevo a su nivel original, como si el efecto sobre los vasos cerebrales fuera también mas prolongado que el efecto general que causa el descenso de la presión sanguínea. Además, los vasos retinianos se dilatan rápidamente a su calibre normal durante la infusión del sulfato de magnesio y que durante el acmé de los síntomas cerebrales parecían adelgazados.

Las dosis de sulfato de magnesio que se usaron son mas grandes que las aconsejadas en general. La concentración mínima efectiva de magnesio en el suero fué aproximadamente de 5 mlgs.% pero en algunos niños tuvo que subirse a 7 u 8 mlgs. La dosis total sugerida por este estudio es de 150 a 200 mlgs. de sulfato de magnesio hidratado por Kg. de peso corporal administrados bajo la forma de solución al 3% (5 a 7 c.c./kg) en el curso de una hora. La mitad de la dosis puede darse generalmente durante los primeros 15 a 20 minutos dependiendo de la presión arterial y la respuesta clínica. Con excepción de enrojecimiento de la piel y sensación de calor, ambos ocasionales, no se presentaron síntomas tóxicos ni depresión del sistema nervioso como respiración lenta, sugiriendo que el control de las convulsiones no sea debido al efecto depresor del magnesio que se nota con concentraciones plasmáticas de magnesio mas elevadas.

En conclusión, se sugiere que en los niños con glomerulonefritis aguda existe espasmo vascular renal y que la terapéutica adecuada con sulfato de magnesio produce su relajación.

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IDIOPATHIC CELIAC DISEASE

I. Mode of Onset and Diagnosis

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AN INVESTIGATION of chronic malnutrition in childhood with special attention to the diseases presenting the celiac syndrome has been in progress since 1939. During this time the authors have seen approximately 200 cases of cystic fibrosis of the pancreas, 100 cases of severe celiac disease, over 300 cases of starch intolerance and a smaller number of cases presenting the celiac syndrome for various other causes. A preliminary report of observations on celiac disease was made in 1947.[1]

A. Selection of Cases for Study: The initial problem in a study of celiac disease is the selection of cases for analysis. Its essential nature is unknown and there is no single clinical or laboratory finding which is pathognomonic. Little disagreement surrounds the diagnosis of patients with prolonged and severe celiac disease. The difficulty arises in patients seen in the early phase of the disease and also in the moderately ill children, for these cases often lack some of the clinical or laboratory features considered by tradition to be essential for diagnosis.

For the present study a group of 58 cases was selected which the authors believe would be generally accepted as cases of idiopathic celiac disease on clinical and laboratory grounds. The patients were assigned case numbers 1 through 58 (table 6) in accordance with the time of admission. Each of the cases selected fulfills all the following criteria:

1. The patient was studied when between the ages of 6 months and 5 years.
2. There was persistent or recurrent diarrhea with large foul bulky stools.
3. Steatorrhea was present during the severe phase of the illness. Fecal fat was determined while the patient was on a diet normal for his age and including whole cow's milk.
4. Abdominal enlargement was present.
5. The muscles were small, weak and flabby.
6. At some time the weight was two standard deviations or more below the normal mean for the age.
7. The patient failed to do well on a normal diet and improved on a diet designed for celiac disease.
8. The duodenal juice showed a normal concentration of trypsin.
9. No anatomic or bacteriologic cause for the diarrhea was found.

Demonstration of steatorrhea was required for inclusion in the series, not only because it is generally considered to be requisite, but because it is a convenient and objective means of separating the mild from the severe cases. A flat glucose tolerance curve or a flat vitamin A absorption test were not required because these tests give different results

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at different times in the same patient. A reduced amylase in the duodenal juice, although usually demonstrable, was not required since the relationship of deficient amylase to the disease requires further study.

B. Clinical Data:

1. Etiology and family history.—Without exception the patients were of white European stock. Of 48 patients for whom data are available, 39 had single predominant racial or ethnic origins, the distribution of which was as follows: Hebrew 21 (so far as is known, all were from Germany, Poland or Russia); Anglo-Saxon 10; Italian 7; Irish 5; Czech 2; German 1. The remaining 9 patients were of mixed European stock. The Negro and oriental races were not represented. Of the 58 patients, 26 were male and 32 female. There was no suggestion that age of the mother or birth weight of the child were of etiologic significance.

TABLE 1

AGE OF ONSET OF GASTROINTESTINAL SYMPTOMS, COMPLETION OF CELIAC "TRIAD,"* AND OF DIAGNOSIS OF CELIAC DISEASE

	Age (mo.)						
	0–3	3–6	6–9	9–12	12–15	15–19	18+
Onset of							
Diarrhea	11	6	20	4	8	3	6
Vomiting	11	6	10	5	3	1	2
Poor gain	4	5	9	10	14	7	9
First symptom	25	7	15	4	6	0	1
Complete celiac triad	0	4	10	7	20	7	10
Diagnosis	0	1	11	10	15	7	14

* Celiac "triad"—diarrhea, weight loss, abdominal enlargement.

Of 48 siblings of patients of the present series, six had evidence of mild or severe celiac disease. Three of these were studied in Babies Hospital. Two were the younger brother and sister of Case 34, and both had intolerance to dietary starch, intermittent diarrhea, large abdomens and amylorrhea, and both responded to a celiac regime. The third was an older brother of Case 32 who had had intermittent diarrhea since infancy, was admitted to the hospital at the age of 4 years and was found to have starch intolerance. The only twin of the series, Case 33, had a normal fraternal twin.

A suggestive history of gastrointestinal disturbances characterized by intolerance to fat, episodes of diarrhea and at times loss of weight was given by 8 parents and 7 other relatives in the families of the 58 patients under consideration. The father of Case 47 had had severe celiac disease as an infant, diagnosed as such in a hospital.

The occurrence of diabetes and celiac disease in the same family has already been recorded.[2] In the present series there was a history of diabetes in the families of nine patients.

2. Age of onset.—Gastrointestinal symptoms were said to date from birth in 15 cases, and began between the first and the sixth month in 17 more, a total of 32 cases or slightly more than half (table 1) with onset in the first half-year.

The complete celiac "triad" (diarrhea, weight loss, abdominal enlargement) did not appear until after the age of 6 months in 54 of the 58 patients. The diagnosis of celiac

disease was rarely made until all the clinical manifestations traditionally required of such patients were present.

Prodromal symptoms of a nonspecific nature and therefore difficult of recognition preceded full-blown celiac disease by weeks or months. Overt onset in nearly every case was an episode of acute diarrhea, most commonly occurring between the sixth and ninth month of life and usually initiated by an intercurrent upper respiratory infection. This was generally followed by a continuation of abnormal stools and loss of weight.

Prodromal gastrointestinal symptoms were of two types (table 1): vomiting and diarrhea.

Vomiting was the initial symptom in 38 of the 58 cases. It was sometimes mild and intermittent, more often forceful and severe and at times the chief presenting complaint. In 11 cases, it began in the neonatal period and in 9 of these no diarrhea was

TABLE 2

EFFECT OF BREAST FEEDING ON AGE OF ONSET OF DIARRHEA IN CELIAC DISEASE

Breast Feeding	Age of Onset of Diarrhea (mo.)							
	Birth—1	1–3	3–6	6–9	9–12	12–15	15–18	over 18
1 wk.	4	4	4	11	4	6	1	2
1 to 7 wk.	1	1	1	6	0	0	0	0
2 to 6 mo.	0	0	1	1	0	2	2	3

Comparison of infants breast fed less or more than 2 mo. with respect to onset of diarrhea before or or after 1 yr. gives X^2 of 12 and P of $<.01$.

present at the time, appetite was preserved and gain in weight fair. Vomiting frequently ceased after the third month and there was then a symptom-free interval until the overt onset of the disease.

Watery diarrhea was almost never present, but the abnormal bowel movements consisted of 3 to 5 bulky, loose, moderately foul stools a day. In 17 cases, abnormal stools were noted before the age of 6 months and in 9 in the neonatal period. By comparison with normal siblings, the stools were described as bulkier, softer and more numerous than normal in the early months of life, even in the cases in which no recognizable diarrhea was recorded until the latter part of the first year.

Poor gain or a loss of weight is a fairly late development. Vomiting, and at times diarrhea, precede it by weeks or months, during which time gain in weight is frequently irregular. Because of the insidious course of celiac disease in its early phase, its initial symptoms being considered of minor scope, many of the patients had been labeled "feeding problems" for some time preceding recognition of the disease.

3. Effect of breast feeding on age of onset of diarrhea.—There is a tradition in both Europe and America that celiac disease occurs chiefly if not entirely in infants who have not been breast-fed.[3, 4] In accord with present custom in New York City, the majority of the infants in the present series were formula-fed from birth; of 54 of the patients whose neonatal feeding is known, 36 received no breast milk or received it for less than a week, 9 received breast milk for a period of 1 to 7 weeks, and the remaining 9 infants received breast milk from 2 to 6 months (table 2). No difference appears in the age of onset of diarrhea between groups receiving breast milk less than a week and those receiving

it from 1 to 7 weeks; these groups were therefore pooled and compared with the group receiving breast milk for more than eight weeks, using one year as the dividing line between earlier and later onset. The difference is highly significant ($X^2 = 12$; $P < 0.01$), giving evidence that the feeding of breast milk for more than two months delays the onset of diarrhea in patients with celiac disease. On the other hand, breast feeding for the first 2 to 6 months does not prevent celiac disease, since this group contains a few such examples of infants who eventually presented severe symptoms.

4. Physical and roentgenographic findings.—Abdominal enlargement, small, weak, flabby musculature and marked malnutrition were required for a patient to be included

TABLE 3

FREQUENCY TABLE OF S.D. FROM MEAN FOR TOTAL BODY LENGTH AS COMPARED WITH HEAD CIRCUMFERENCE IN PATIENTS WITH SEVERE CELIAC DISEASE

	Standard Deviations from Mean*					
	A. Total Body Length					
Age	+1 to 0	0 to −1	−1 to −2	−2 to −3	−3 to −4	−4 to −5
6–12 mo.	2	4	1	2	0	1
12–18 mo.	2	6	10	7	1	2
18–24 mo.	3	2	5	3	1	3
24–30 mo.	0	3	3	5	5	1
30–36 mo.	0	1	1	2	0	1
3–4 yr.	1	3	1	3	4	1
4–5 yr.	0	1	4	2	1	0
	8	20	25	24	12	9
	B. Head Circumference					
6–12 mo.	1	2	3	5	5	3
12–18 mo.	2	5	5	6	3	3
18–24 mo.	2	2	4	5	4	2
24–30 mo.	1	4	2	5	2	1
30–36 mo.	1	2	0	1	2	0
3–4 yr.	4	2	3	4	0	0
4–5 yr.	2	4	3	1	0	0
	13	21	20	27	16	9

* Normal for length from Simmons and for head circumference from Vickers and Stuart.

in the present series. Most physical findings therefore were in accord with traditional descriptions.

No clinical or roentgenographic evidence of rickets or scurvy was found in the present series. Roentgenographically, however, osteoporosis of some degree occurred in all patients. Bone maturation, as estimated by roentgenograms of the hand, was delayed in varying degree in 22 of 41 cases. The teeth erupted at the regular times in the majority of cases, but in a few, marked delay was present. Roentgenographic examination of the gastrointestinal tract was performed in 45 cases, in all of which small intestinal motility was found to be abnormal.

Growth in height is retarded or arrested during the severe phase of celiac disease. Such retardation applies equally to the skull, as evaluated by the head circumference, especially in the case of younger patients who are severely ill at an age when the growth of the head is rapid. It has not been generally realized in the past that this may lead to a disproportion between measurements for the total length of the body and the head circumference. Failure to recognize this fact has led to an erroneous diagnosis of cerebral hypoplasia on more than one occasion.

Table 3 shows the degree of retardation in growth of patients with celiac disease, as compared with healthy subjects of the same age. Total body length and head circumference are recorded in terms of deviation, in multiples of the standard deviation, from the norm for narrow age segments. It is apparent that severe retardation in growth of the cranium may occur at a younger age than severe retardation in height. At 6 months or one year of age, the head circumference may be as much as 5 S.D. below the mean in infants who later develop normal head measurements and normal intelligence.

C. Evaluation of Laboratory Procedures as Aids in Diagnosis: No single clinical feature or laboratory finding is pathognomonic of celiac disease or found exclusively in this condition. However, certain tests give abnormal results in a majority of patients and it has become customary to require their presence as essential diagnostic criteria. The data obtained from the present series of cases have been analyzed in an attempt to evaluate the reliability of some of the tests commonly used in the diagnosis of celiac disease. Procedures included in the study are the following:

1. Assay of trypsin and amylase in the duodenal juice.
2. Oral glucose tolerance curves.
3. Serum protein levels.
4. Fecal fat determination by chemical methods on three day stool collections and demonstration of excess fecal fat on microscopic examination of the stools.
5. Fasting serum vitamin A and carotene levels and vitamin A absorption curves.

1. Assay of pancreatic enzymes in the duodenal juice.—This procedure was performed in all cases to rule out fibrocystic disease of the pancreas by the demonstration of normal trypsin levels in the duodenal juice. Methods employed were described previously.[5]

a. Trypsin.—In all patients except one, Case 38, the trypsin assay was more than 100 viscosimetric units/cc. Save for this one exception, trypsin values ranged from 112 to 1040 viscosimetric u./cc., with 47 of the 58 determinations lying between 200 and 600 u./cc. (table 4). The higher figures approximate those of undiluted activated pancreatic juice; dilution by intestinal and gastric content appears to explain these wide variations in trypsin values. The great majority of patients with cystic fibrosis of the pancreas have a trypsin content of the duodenal juice of less than 10 u./cc.

Case 38 was included in the present series of patients with celiac disease despite the low level of trypsin in the duodenal juice (57 u./cc.), because the fecal fat content became normal with clinical improvement (table 6); the authors have never observed disappearance of steatorrhea on a normal fat intake (40 to 70 gm./day) in cases of fibrocystic disease.

While trypsin assay of the duodenal content is a reliable determination, care has to be exercised to avoid certain possible sources of error. These can be listed as follows:

First, trypsin activity is lost in a few hours when duodenal juice is allowed to stand at room temperature. This loss of potency occurs rapidly if the juice is acid or diluted with distilled water. For this reason all trypsin determinations were performed as soon

TABLE 4

TRYPSIN AND AMYLASE IN DUODENAL JUICE; FIRST ASSAY IN EACH CASE
PATIENTS NOT IN CRISIS

	Trypsin, u./cc.								
	<100	100–200	200–300	300–400	400–500	500–600	600–700	700–800	>800
No. of Cases	1	10	11	6	13	5	5	2	5

	Amylase, u./cc.								
	<20	20–40	40–60	60–80	80–100	100–120	120–140	140–160	160–180	>180
No. of Cases	16	17	11	3	2	5	0	1	1	2

	No. of Cases Ratio Amylase/Trypsin×100								
Age	<5	5–10	10–15	15–20	20–25	25–30	30–35	35–40	>40
6–12 mo.	8	5	2	1	0	2	1	0	0
1–5 yr.	10	8	9	2	2	1	1	3	3

Mean of controls 6 mo. to 5 yr. of age (5): Trypsin 235 u./cc., Amylase 178 u./cc., A/T ratio×100 =75%.

as possible after duodenal material had been obtained, and dilution with distilled water carried out immediately prior to the assay.

Second, the trypsin content of the duodenal juice may be low if the material is not obtained from the proper site, near the ampulla of Vater. To avoid this the position of the duodenal tube was checked by fluoroscopy in all cases.

Third, a temporary depression of trypsin may occur in severe dehydration and in acutely ill or marantic infants. The pancreatic enzymes will in these cases return to normal a few days later when the patient's clinical condition has improved. This sequence of events was shown to have occurred in three patients reported some years ago[5] and has been demonstrated in five cases in the present series. To avoid this source of variation, duodenal drainage was performed in all instances after the clinical condition had improved and the patient stabilized.

b. Lipase.—Pancreatic lipase has repeatedly been shown to be within normal limits in celiac disease.[5,6] For this reason and because chemical determination of this enzyme is much less reliable than that of trypsin and amylase, lipase was determined in only 31 of the 58 cases in the present series. In these patients the figures obtained fell within normal range.

c. Amylase.—Pancreatic amylase activity of the duodenal juice was determined in viscosimetric u./cc. A more convenient way of expressing the amylase values is found in the ratio amylase/trypsin x 100 (the A/T index), which in ordinary circumstances remains quite constant on repeated determinations in the same patient.[1] The previously mentioned variable degree of dilution of the pancreatic juice by gastric and intestinal contents affects the absolute concentration of amylase but not the index.

Since amylase is somewhat more stable than trypsin when duodenal juice stands for several hours at room temperature or is diluted with water, the error from degradation of trypsin tends to increase the index. By prompt performance of assays, errors were kept to a minimum.

In normal infants pancreatic amylase is absent or nearly so in the first few months of life. It is present at low levels between 6 months and 1 year and does not reach adult levels of concentration until the second year of age.[5] As a working rule, the normal A/T index was considered to be 20 or more between 6 months and 1 year and 40 or more above this age. These figures are conservative since the mean A/T index in control subjects was found to be 45 between 6 months and 1 year, 67 between 1 and 2 years, and 175 between 2 and 5 years of age.

Duodenal juice amylase index was abnormally low in 52 of the 58 celiac cases (table 4). A reduced pancreatic amylase in the presence of normal pancreatic trypsin and lipase is thus present in the majority of cases of severe celiac disease.[1,7,8] This same finding also occurs in most patients with mild celiac disease (starch intolerance).[1] As such, it affords valuable confirmatory evidence in the diagnosis of celiac disease and is at least as useful as some of the other traditionally acceptable tests. No claims, however, are made for its infallibility. Indeed, it has been shown that a low pancreatic amylase occurs in a small percentage of normal individuals, while on the other hand, the finding of normal levels of this enzyme in the duodenal content does not, according to present knowledge, invalidate the diagnosis of celiac disease if all other clinical and laboratory evidence tends to confirm it. A reduced pancreatic amylase has been observed in this laboratory in patients with nephrosis (8 out of 11 patients) and in cases of severe eczema. A common denominator between these conditions and celiac disease is a tendency to hypoproteinemia, but what, if any, is the relation between this finding and a reduced pancreatic amylase is not known.

2. Glucose tolerance curves.—The tradition that the glucose tolerance curve is always flat in celiac disease stems from the observations of MacLean and Sullivan[9] in 14 cases and of Svensgaard[4] in 5 cases. Since their work, it has generally been considered that a flat glucose tolerance curve is a primary feature of the disease and essential for diagnosis. There is, however, no agreement as to the point of failure of the mechanism of glucose absorption and utilization. The pattern of the curve of blood sugar following the intravenous administration of glucose has been found normal by several observers.

Various explanations of the failure of normal rise in blood sugar after ingestion have been given: 1. retention of the glucose in the stomach because of hypomotility[10]; 2. failure of absorption by the intestinal mucosa[11] because of impaired phosphorylation; 3. normal absorption but rapid utilization so that the blood level is not permitted to rise normally.[4,12] To these may be added a fourth possibility, based on the observation that interference with the salt and water balance either directly or by adrenalectomy may result in a flat glucose absorption curve,[13] and a fifth, that abnormal interestinal motility may delay absorption from the intestine. The varying interaction of some or most of these factors is presumably responsible for the abnormal results of the oral glucose tolerance curves seen in many patients with celiac disease.

Oral glucose tolerance curves were carried out during the severe phase of the disease or shortly thereafter in 28 cases. Two or more tests were performed in several patients, making a total of 34 observations. Total blood sugar was determined in all instances by Benedict's micromethod.[14] After a fasting sample was obtained, glucose 1.75 gm./kg.

body weight was fed and samples of capillary blood obtained at ½, 1, 2 and 3 hour intervals. In a few of the earlier determinations the half-hour sample was omitted. In no case was the test performed while the patient was dehydrated or on intravenous feedings only, but in some instances the test was carried out shortly before or after a period of crisis.

Of the 34 curves, the rise in blood sugar above fasting level was less than 10 mg./100 cc. in 10 (flat curve), between 10 and 40 mg./100 cc. in 11 (low curve), and over 40 mg./100 cc. in 13 (normal curve) (Fig. 1). During the severe phase of the disease, the curve was therefore flat or low in about two-thirds of the cases and within normal range in the remaining third. In some instances a normal curve was obtained from patients who were severely ill and presented all the classical characteristics of celiac

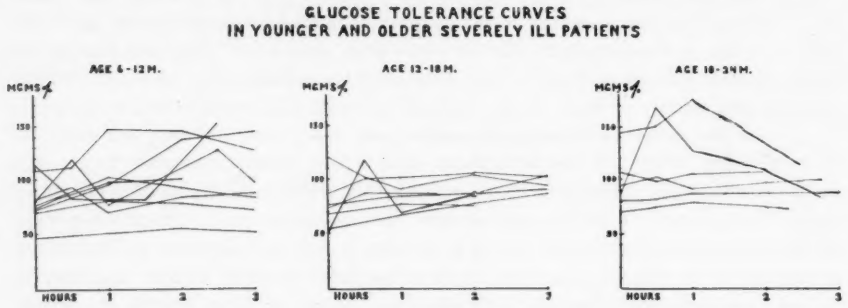

FIG. 1

disease, including steatorrhea and response to appropriate therapy. In more than one such case, therapy had been withheld by the referring physician or hospital because a flat glucose tolerance curve was considered necessary for the diagnosis of celiac disease as, for example, in Case 47.

It was evident from a study of the data that a normal curve could be obtained at any period of the disease with the possible exception of episodes of dehydration necessitating intravenous therapy. Analysis of the data with respect to the age of the patient suggested that a flat oral glucose tolerance curve was a more consistent finding in the older children than in young infants.

Glucose feeding is well tolerated and the weight curves show a rapid rise when a large proportion of the caloric requirement is provided as glucose. It is apparent that glucose absorption must be fairly complete even if slow.

3. Serum protein levels.—Determination of the serum protein concentration has proved of assistance in both diagnosis and prognosis of celiac disease. This determination was performed in 52 of the 58 cases in the present series by micro-Kjeldahl method. The results are charted in table 5. If 6.0 gm./100 cc. serum is taken as the lower level of normal during the first year of life,[15] and 6.5 gm./100 cc. as the lower limit of normal thereafter, only 7 of the 53 celiac patients had a normal serum protein level when first admitted. Edema of moderate degree was present in several of these cases. Serial determinations revealed a slow increase in serum protein levels during the period of clinical improvement.

Total serum protein is an important indication of severity of the disease and of im-

TABLE 5A

TOTAL SERUM PROTEIN ON HOSPITAL ADMISSION; FREQUENCY CURVE OF FIRST DETERMINATION IN 52 CASES

	Total Serum Protein (gm./100 cc.)								
Age	<3.0	3.0–3.5	3.5–4.0	4.0–4.5	4.5–5.0	5.0–5.5	5.5–6.0	6.0–6.5	>6.5
6–12 mo.	0	0	1	0	4	5	4	2	2
1–2 yr.	1	1	1	0	4	4	7	7	3
2–5 yr.	0	0	0	1	0	2	1	1	1
Total	1	1	2	1	8	11	12	10	6

pending crisis. In the authors' experience "celiac crises" with sudden dehydration and acidosis do not occur as long as the serum protein level remains normal. A level of total serum protein below 5.0 gm./100 cc. indicates an unstable balance which can be easily upset by an intercurrent upper respiratory or other infection. Serum protein determinations were performed in 22 of 24 patients shortly before or after a "celiac crisis"

TABLE 5B

TOTAL SERUM PROTEIN DURING CRISIS ABD BEFORE PARENTERAL THERAPY

	Total Serum Protein (gm./100 cc.)						
No. of cases	<3.0	3.0–3.5	3.5–4.0	4.0–4.5	4.5–5.0	5.0–5.5	>5.5
	1	2	2	1	10	8	0

and levels below 5.5 gm./100 cc. were found in all, in one instance ranging even below 3.0 gm. The albumin fraction was found to be less than 4 gm. in the 11 cases in which it was determined.

Determination of total serum protein is also of assistance in differential diagnosis. While normal findings do not rule out celiac disease, reduced levels are confirmatory and make the diagnosis of cystic fibrosis of the pancreas improbable. In the latter condition, serum protein levels have almost invariably been normal after the age of 6 months, in the patients seen in this clinic.

4. Fecal fat determination by chemical methods on three-day stool collections and on microscopic examination of the stools.—For inclusion of a patient in the present series, it was required that increased fecal fat excretion be demonstrated by chemical analysis of stools collected over a three-day period or by an obvious excess of fat droplets or crystals on microscopic examination. Individual determinations for the 58 patients with celiac disease under consideration are recorded in table 6. A level of excretion of 3 gm./24 hours[16] was taken as the upper limit of normal for the present series of patients, all of whom were offered diets containing from 50 to 70 gm. of fat per day.

Twenty-nine of the 42 cases in which chemical analysis of stools collected over a three-day period was done, had a fecal fat excretion of more than 3 gm./24 hours. The highest figure was 31.7 gm./24 hours in Case 8 (an intestinal absorption of only 50% of the dietary fat intake). This little boy was very sick at the time and subsequently died.

Five other patients who failed to show a fecal fat excretion of more than 3 gm./24

TABLE 6

FECAL FAT, SERUM CAROTENE AND VITAMIN A

Case No.	Sex	Age (mo.)	Fecal Fat			Serum Carotene (μ/100 cc.)	Serum Vitamin A (I.U./100 cc.)	
			Per Cent* of Dry Weight	Gm.*/24 hr.	Microscopic		Fasting	Maximal Rise Above Fasting in Absorption Test
1	M	7	—	—	3+	—	—	—
2	F	13	—	—	3+	2	28	0
3	F	16	30	6.1	3+	—	—	—
4	F	4	—	—	3+	—	—	—
5	M	36	44	15.1	—	0	120	10
6	M	18	37	3.3	0	—	—	—
7	M	12	16	3.5	—	—	—	—
8	M	20	41	9.9	—	7	—	—
		21	45	31.7	—			
9	F	12	69	6.6	—	40	47	29
10	F	9	21	3.1	—	—	—	—
11	F	16	34	3.8	0	11	29	45
		24	11	1.1	0			
12	F	46	24	7.9	3+	16	123	175
		48	17	2.8	1+			
13	F	10	—	—	4+	22	128	0
		13	12	1.3	—			
14	F	22	57	1.7	4+	7	17	16
		35	21	3.7	1+			
15	M	10	41	5.3	—	7	107	59
		21	12	1.0	1+			
16	F	20	27	3.9	3+	5	150	73
17	M	19	8	3.2	1+	0	70	210
		20	11	1.0	2+			
18	F	42	44	6.0	4+	5	43	85
		48	25	2.6	1+			
19	F	7	43	6.6	4+	0	54	290
		8	17	2.1	0			
20	M	10	22	7.0	0	0	45	57
21	M	13	44	10.5	1+	0	78	12
22	F	17	30	2.1	2+	1	93	388
		18	25	2.5	2+			
23	M	16	32	4.9	1+	15	66	—
24	M	11	41	1.2	3+	6	116	46
25	F	9	29	1.9	3+	2	78	148
26	F	20	—		3+	0	32	132
		21	6	0.4	0			
27	M	7½	31	5.9	3+	0	56	—
		9½	27	4.2	3+			

* Average of 3 day stool collection.

TABLE 6—(*continued*)

Case No.	Sex	Age (mo.)	Fecal Fat			Serum Vitamin A (I.U./100 cc.)		
			Per Cent of Dry Weight	Gm.*/24 hr.	Microscopic	Serum Carotene (μ/100 cc.)	Fasting	Maximum Rise Above Fasting in Absorption Test
28	M	17	—	—	3+	—	—	—
29	F	13	—	—	3+	—	—	—
30	F	42	8	2.85	4+	0	—	—
31	F	21	—	—	4+	50	127	—
		22	16	0.87	2+			
32	M	11	—	—	4+	—	—	—
		13	13	0.64	0			
33	F	18	31	—	4+	0	8	—
		19	35	2.1	0			
34	M	36	—	—	3+			
		37	22	2.0	—	—	—	—
35	F	31	29	5.5	1+	0	192	—
36	M	10	—	—	4+	0	104	—
		11	39	4.8	—			
37	M	16	32	1.5	3+	0	68	—
38	M	21	37	1.63	—	0	66	—
39	F	29	25	3.82	4+	—	—	—
		34	32	4.66	0			
40	F	9	42	5.6	1+	0	42	—
		18	15	2.8	0			
41	M	35	23	4.5	0	0	24	42
42	M	12	—	—	4+	0	66	—
43	F	36	—	—	3+	—	—	—
44	F	19	—	—	4+	0	106	—
		21	13	0.9	0			
45	F	22	47	6.9	4+	0	86	—
		23	37	5.8	3+			
46	F	11	57	4.1	4+	0	56	0
47	F	13	—	—	3+	0	48	0
48	F	11	—	—	4+	0	0	—
49	F	11	—	—	4+	0	66	—
50	M	14	—	—	3+	—	—	—
51	M	8	—	—	4+	0	0	—
52	F	13	—	—	4+	0	64	—
53	F	13	27	3.4	3+	0	80	—
54	F	23	—	—	4+	—	—	—
55	M	10	—	—	4+	0	38	—
56	M	10	—	—	4+	0	30	—
57	M	15	32	3.6	4+	28	62	72
58	M	32	—	5.0	3+	0	114	—

hours were nevertheless retained in the series because of an abnormally high proportion of fat in the three-day stool collection (more than 30% of the solid matter).

While the proportion of fat in fecal dry matter is no longer generally accepted as a reliable index of steatorrhea,[16, 17] there are, however, exceptions. There are instances of patients with celiac disease who are acutely ill and almost completely anorexic in whom the abnormal fecal fat excretion is represented by a high fat percentage of fecal solids despite the fact that the actual value in grams is low because the oral intake is almost nil. A good example of such a patient is Case 14, R.T., one of the most severely ill patients in the series on admission, who weighed less than 6 kg. at 22 months of age. During the first three-day stool collection, she was markedly anorexic and fecal fat comprised 57% of dried feces, although the daily excretion of fat was only 1.7 gm./24 hours. Some months later when she had greatly improved and was eating well, fecal fat was only 21% of dry matter, but 3.7 gm./day.

Twenty-four cases, otherwise typical, were included in the series because microscopic examination of the stools was accepted as evidence of steatorrhea. The present authors' observations have shown good correlation between microscopic and chemical examination.[16] It has been found a useful screening test provided its limitations be kept in mind.

In 13 of the 42 cases in which chemical estimation of fecal fat on three-day stool collections was performed, the determination was repeated a second time, in most instances after clinical improvement had occurred. In eight cases there was a return to normal of the figures for fecal fat excretion. This agrees with previously reported observations[1] that steatorrhea frequently disappears with improvement in the patient's condition.

5. Serum carotene and vitamin A levels and vitamin A absorption curves.—Serum carotene and vitamin A levels were determined by the antimony trichloride method described by Clausen and McCoord[18] using a photoelectric colorimeter. According to May and collaborators[19] in a series of 50 normal children between the ages of 1 and 12 years, normal values were as follows: for serum carotene an average level of 80 γ/100 cc., with a range of 40 to 130 γ; for fasting serum vitamin A, an average level of 56 I.U. (international units)/100 cc., with a range of 30 to 100 I.U.

Results of determinations made shortly after the first admission in 44 of the 58 patients are given in table 6. In it is also recorded the maximal rise in serum vitamin A above the fasting levels after ingestion of a test dose of the vitamin in 21 of the 58 cases. In 13 patients the maximal rise took place 4 to 6 hours after administration of oleum percomorphum, in the remainder it occurred at 12 to 24 hours.

Determination of single serum levels of vitamin A was found not to be useful in diagnosis, because the results were so often within the normal range or high despite the presence of steatorrhea and the complete absence of serum carotene. This finding reflects the fact that when enough preformed vitamin A is administered orally, the serum vitamin A levels are within normal limits despite increased intestinal fat excretion. These normal serum values correlated with the complete absence of clinical evidence of vitamin A deficiency.

In contrast, single determinations of serum carotene were found useful inasmuch as they bore good relation to the presence of increased fecal fat excretion. Of 44 patients in the present series in whom this test was performed when first admitted, serum carotene was below the lower level of normal (40 γ/100 cc.) in 42 and in 37 below the very low level of 10 γ/100 cc. In 27 patients no carotene at all was found in the serum. In Case 31 the serum carotene level of 50 γ was determined some time after admission when the

child had improved clinically and the steatorrhea decreased, as shown by a fecal fat excretion of only 0.87 gm./24 hours. Similar considerations could be applied to the other four patients who, while below normal, had levels above 10 γ/100 cc. It can therefore be stated that in patients who have been receiving a normal diet, single serum carotene levels are informative as screening procedures for the presence or absence of steatorrhea. These findings confirm the impression of other authors as to the value of this determination.[20]

Vitamin A absorption tests were performed according to the method described by May and McCreary,[20] vitamin A 7000 I.U. being given orally in the form of oleum percomorphum and blood samples drawn for vitamin A determination as follows: Control, 4, 6, 12, 24 hours after ingestion of the test dose of the vitamin. The calculated dose of oleum percomorphum was given to a fasting patient simultaneously with a breakfast containing milk, butter and one egg. The importance of the type of breakfast and the use of pancreatin in conditioning the results of the vitamin A absorption test have been previously shown.[21, 22] Following the test meal, the patients received a regular diet. Carrots were omitted two days previous to the one appointed for the test. According to May and McCreary[20] and Cienfuegos,[23] the serum vitamin A level should normally rise more than 200 I.U./100 cc. above the fasting level in 4 to 6 hours after ingestion of the test dose.

In the present series of cases, vitamin A absorption curves were obtained in 28 patients. A rise of more than 200 I.U./100 cc. serum was observed in 3 instances, of 100 to 200 I.U. in 3, of 50 to 100 I.U. in 5, and of less than 50 I.U. in 10 cases. Study of the clinical records reveals a trend toward a low rise when the test was performed during the acute phase of the illness and a rough correlation with the presence of steatorrhea.

In recent years the vitamin A absorption curve has been used as a means of differential diagnosis between idiopathic celiac disease and cystic fibrosis of the pancreas.[22, 24] There is general agreement that patients with fibrocystic disease of the pancreas absorb the vitamin A better in alcohol than in ester form, and that many patients with severe celiac disease absorb both forms less well than normal. Poor absorption of vitamin A has been shown, however, to be present in a variety of conditions[24] and a flat vitamin A absorption curve is by no means diagnostic of celiac disease. Because of the inconsistent results in celiac patients and because of the amount of blood required for determination, the vitamin A absorption test is not recommended as a routine diagnostic procedure.

D. Differential Diagnosis:

The diagnosis of celiac disease is usually first suspected on the appearance of the celiac "triad" of persistent diarrhea, loss of weight and an enlarged abdomen. Laboratory means are then used to rule out other causes of this clinical picture and to provide support for the diagnosis by the demonstration of phenomena commonly found in celiac disease. Many patients sent to the authors with the provisional diagnosis of celiac disease on the basis of the clinical picture were found to be suffering from other maladies; in this group the more frequent final diagnoses were as follows:

1. Cystic fibrosis of the pancreas. This presents a problem in the younger infants with congenital pancreatic deficiency who may have intermittent diarrhea, hypoproteinemia and hydrolability. In the authors' experience, these clinical phenomena rarely occur after the sixth month. The frequency of respiratory infection in both diseases and the occasional occurrence of partial pancreatic deficiency lead to difficulties.

2. Starvation or improper feeding may result in a clinical picture resembling celiac

disease. These patients respond to normal feeding and an improved environment. Underfeeding for economic reasons has not been encountered in this study.

3. Primary mental retardation with or without a demonstrable anatomic basis may present a difficult problem in diagnosis, because of failure to gain and poor feeding. This is a more frequent problem at present than in the past because with less breast feeding the earlier onset of celiac disease may result in apathy, delayed motor development and temporary microcephaly. The diagnosis rests on demonstration of an anatomic or physiologic basis for mental retardation or by a dramatic response to a celiac regime. Among the final diagnoses recorded are: porencephaly; encephalomyelitis; congenital dysfunction of the central autonomic nervous system.

4. Lipoid storage diseases may result in steatorrhea and physical retardation. Gaucher's disease and Niemann-Pick's disease have been encountered in patients admitted with the provisional diagnosis of celiac disease.

5. Congenital megacolon may be complicated by intermittent diarrhea, steatorrhea, and chronic respiratory infection, and may therefore simulate celiac disease or fibrocystic disease of the pancreas, especially in infancy.

6. Congenital malformation of the intestine, including either malrotation or stenosis may simulate celiac disease in infancy.

7. Chronic enteric infection with parasites or pathogenic bacteria occurs in patients with celiac disease or it may occur in otherwise normal infants and simulate this condition. The diagnoses must be established independently; celiac disease may be suspected in patients who continue to have symptoms after the infection has been eliminated.

8. Intestinal allergy is, in the authors' experience, an uncommon cause of the celiac syndrome. The intolerance of most patients with celiac disease for raw milk is often erroneously considered due to milk allergy in spite of excellent clinical response to a formula of protein milk. Intestinal allergy may be suspected following failure of the infant to respond to dietary therapy of protein milk and adequate supplements.

9. A few early cases of ulcerative colitis may be encountered in young children. The relationship of childhood ulcerative colitis and celiac disease deserves future study.

Discussion

The etiology of idiopathic celiac disease is still not clearly known, but evidence has been accumulating that there is in this condition an hereditary constitutional defect in metabolism or physiology which persists after the clinical manifestations of the severe illness have disappeared.[1] Diagnosis is not difficult in patients with long-standing disease who have developed all the classical manifestations of the celiac state. However, the existence of many milder cases lacking some of the features leads to uncertainty as to the validity of traditional requirements and frequent difficulties in recognition of individual cases.

Many features which were prominent in earlier reports but are now rarely seen are recognized as expressions of nutritional deficiency, such as, for instance, scurvy and rickets. On the other hand, celiac disease has at the present time a much earlier onset than in former years. Consideration of present feeding practices in the United States suggests that early artificial feeding and universal use of vitamin supplements account for most of the differences between the clinical picture of celiac disease as now seen in this country and the classical descriptions in the British and continental literatures.

No single test is pathognomonic of idiopathic celiac disease, and diagnosis should be

based on the clinical and laboratory picture as a whole and not on the presence or absence of single factors. In practice, the diagnosis is first suspected on clinical grounds in patients presenting the celiac "triad" of persistent diarrhea, loss of weight, and an enlarged abdomen. Laboratory means are then applied to rule out other causes of this clinical picture or to provide support for the diagnosis of idiopathic celiac disease. Clinical trial of the response to a therapeutic dietary regime effective in celiac disease also provides important confirmatory evidence.

Among the laboratory determinations commonly applied in the study of a patient suspected of having celiac disease are cultures of the stools, duodenal drainage and roentgenographic examination of the gastrointestinal tract. In the present studies, the most consistent positive support for the diagnosis of severe celiac disease was provided by a low serum protein concentration, a low duodenal amylase, a low serum carotene and an increased fecal fat. Greater variability was found in the glucose tolerance and vitamin A absorption curves.

Summary

The acute phase of idiopathic celiac disease was studied in 58 patients. The criteria for selection of these cases are stated.

The frequency and severity of gastrointestinal symptoms in siblings and other relatives appeared to exceed expectation unless the disease is familial.

In the majority of patients studied, symptoms began before the age of 6 months, in 14 at birth. Vomiting was a frequent prodromal symptom. Breast feeding for more than two months was shown to delay the onset of diarrhea. The early onset of symptoms in the present series is believed to be related to the prevalence of formula feeding from early infancy in New York City at present.

Severe retardation in growth of the skull was common and occurred at an earlier age than retardation in height. This, at times, led to disproportion between measurements for total body length and head circumference. Ultimate head measurements were normal.

The following laboratory procedures were performed in the patients under consideration and their results recorded: pancreatic trypsin and amylase estimation on duodenal drainage, glucose tolerance tests, fecal fat determination, total serum protein, serum carotene and vitamin A levels and vitamin A absorption test. The diagnostic usefulness of these procedures is discussed.

Various diseases of infancy which may lead to an erroneous diagnosis of idiopathic celiac disease are discussed.

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SPANISH ABSTRACT

Enfermedad Celiaca Idiopática
I. Forma de Principio y Diagnóstico

Los autores estudiaron la fase aguda de la enfermedad celiaca idiopática en 58 pacientes que fueron seleccionados segun el criterio siguiente: edad entre 6 meses y cinco años, diarrea recurrente o persistente con abundantes evacuaciones fétidas y voluminosas, esteatorrea durante la fase severa de la enfermedad, distensión abdominal, músculos pequeños débiles y blandos, disminución de peso hasta de 2 o más desviaciones standar abajo del promedio normal para la edad, durante alguna época de la enfermedad, intolerancia de la dieta normal y mejoría con dieta para celiaco, concentración normal de tripsina duodenal y ausencia de causa anatómica o bacteriológica para explicar la diarrea.

La frecuencia y severidad de los síntomas gastrointestinales en hermanos y otros parientes pareció exceder lo que se esperaba a menos que la enfermedad sea familiar.

En la mayoría de los pacientes estudiados, los síntomas se iniciaron antes de los 6 meses de edad, en 14 de ellos desde el nacimiento. El vómito fué un síntoma prodrómico frecuente. La alimentación materna durante un tiempo mayor de dos meses parece retardar el principio de la diarrea. Se cree que el principio temprano de los síntomas en esta serie de enfermos esté en relación con la predominancia actual de la alimentación artificial desde la época temprana de la infancia en la ciudad de Nueva York.

Fué común el retardo severo del crecimiento del cráneo y ocurrió a una edad mas temprana que el retardo en estatura. Esto, a veces, originó la falta de proporción entre las medidas de la longitud total del cuerpo y el perímetro cefálico. Las medidas posteriores de la cabeza fueron normales.

Se hicieron las siguientes determinaciones de laboratorio: tripsina pancreática y amilasa del drenaje duodenal, curvas de tolerancia de la glucosa, grasa fecal, proteínas séricas totales, caroteno del suero y niveles y curvas de absorción de la vitamina A.

No existe una sola prueba de laboratorio patognomónica de la enfermedad celiaca idiopática y el diagnóstico debe basarse en el cuadro clínico y de laboratorio en su conjunto y no la presencia o ausencia de factores aislados. En la práctica, el diagnóstico se sospecha primeramente por el cuadro clínico en enfermos que presentan la "triada celiaca" de diarrea persistente, pérdida de peso y abdomen protuberante. A continuación deben usarse los procedimientos de laboratorio para descartar otras causas de este cuadro clínico o suministrar el respaldo al diagnóstico de enfermedad celiaca idiopática. La prueba clínica de mejoría con dieta especial para el celiaco es una prueba confirmatoria importante. En esta serie de enfermos el respaldo positivo mas firme para el diagnóstico de enfermedad celiaca severa fué dado por el bajo nivel de las proteínas del suero, amilasa duodenal baja, caroteno del suero en cifras bajas y aumento de la grasa fecal. Se encontró gran variabilidad en las curvas de tolerancia a la glucosa y de absorción de vitamina A.

Varias enfermedades de la infancia pueden originar un diagnóstico erróneo de enfermedad celiaca idiopática como la enfermedad fibroquística del pancreas, desnutrición, retardo mental primario, lipidosis, megacolon congénico, malformaciones congénitas del intestino, enteritis crónica parasitaria o bacteriana y algeria intestinal.

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IDIOPATHIC CELIAC DISEASE

II. Course and Prognosis

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THE ultimate outlook of patients with celiac disease has always been a subject of interest to the pediatrician. However, the information at hand, for the most part, dates back many years and stems in large measure from other countries. Previous experience was summarized in England by Hardwick[1] in 1939. Only one paper on this subject has appeared in the last 12 years.[2] During this time better knowledge of nutritional requirements, effective control of intercurrent infections by chemotherapeutic and antibiotic agents, and improved methods of parenteral therapy have greatly affected the outcome. It is proposed in this report to present material accumulated over several years, bearing on the course, prognosis and ultimate outlook of patients with idiopathic celiac disease.

MORTALITY AND COURSE OF THE DISEASE

Of the 58 patients previously described,[3] three died as direct or indirect result of celiac disease. The immediate cause of death was a transfusion accident in one case (Case 47),* and chronic failure to provide an adequate caloric intake in the two others (Cases 8 and 45). The expected response to therapy failed to appear in all three and a prolonged period of hypoproteinemia was present before death.

No fatality occurred during "celiac crises," with their sudden dehydration and acidosis, although such episodes were noted in 35 of the 58 cases. It is interesting to note that "celiac crises" were not seen in children over two years of age, presumably because of the increasing stability in water and electrolyte balance with advancing age.

Fifty-five of the 58 cases went on to improvement and clinical recovery. All patients followed a similar clinical pattern, but with great variations in the duration of single phases.

Improvement after beginning dietary therapy was rapid and characterized by marked gain in weight, voracious appetite and return to normal of some tests. The gain in weight was often so great that patients became obese. Throughout this time the stools generally remained abnormal and fairly strict dietary therapy had to be continued. The length of this "stage of rapid improvement" varied in direct proportion to the duration of symptoms prior to therapy, but usually fell between 6 months and 2 years. In most cases it was over by the age of 2 or 3 years.

Following these rapid, often dramatic, changes in the patient's clinical condition, improvement continued at a slower pace for several months or years, ending in most

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* All case numbers in arabic numerals refer to the series of 58 patients with idiopathic celiac disease described in a previous report.[3]

instances in complete or almost complete remission of clinical symptoms. Weight gain and appetite decreased and returned to normal. Bowel movements gradually improved in character, but bouts of diarrhea with the typical stools of celiac disease were common following upper respiratory infections or episodes of dietary indiscretion. Periods of constipation frequently followed these episodes of diarrhea.

"Latent Phase" of Idiopathic Celiac Disease

Twenty-three patients, including 20 of the series of 58 previously described[3] and three additional ones, were admitted to the hospital for re-evaluation 3 to 11 years after original admission. The patients ranged from 5 to 13 years of age.

Pertinent clinical and laboratory data are summarized in table 1. In this table the cases are arranged according to date of birth and are assigned case numbers from I to XXIII in roman numerals. The arabic numerals in the second column refer to the case number assigned to the patient in the series of 58 cases previously reported.[3]

Of the 23 patients, 17 were females and 6 males. No special significance is attached to this sex distribution. In 21 cases the onset of celiac disease was recognized before the age of 2 years, and only in Cases I and VIII were the symptoms recognized at a later age, 6 and 3 years, respectively. The duration of symptoms before the first admission varied from a few weeks to several years.

1. Clinical Findings: When re-evaluated, all patients were leading normal lives and, almost without exception, taking part in all activities appropriate to their ages. In 10 cases, the patient's appearance, his growth and development, and the normal character of his stools were such that the illness was thought to have disappeared completely. Only in Cases I, III, IV and VII was the patients' course not considered entirely satisfactory. Growth and development were seriously retarded only in Cases I and IV (table 1).

In 13 cases the stools were not completely normal, the commonest story being that of episodes of diarrhea following dietary indiscretion or upper respiratory infections. Meteorism and abdominal pain were rather frequent complaints.

Appetite was excellent in seven cases, was reported as being poor in only one, and good to fair in the others. The diet was markedly restricted as to fat intake in at least 15 of the 23 cases. This was voluntary in most instances, although habit unquestionably played a part in food selection. Most patients had a moderate or normal intake of starchy foods.

2. Hematologic Findings: Of 14 patients for whom data were available, 10 had moderate to marked hypochromia (table 2A). In four instances (Cases II, VIII, XV, XXIII), the mean cell volume was greater than 100 cm.^{3}, more than two standard deviations above the mean for the age.[4] This macrocytosis was accompanied in all four patients by hypochromia of significant degree.

Peripheral blood smears were characterized by great variability in size and hemoglobin content of the single red cells. The bone marrow was examined in several cases, but no abnormal findings were noted.

In table 2B are recorded serial blood counts done on two patients (Cases XV and XXIII), suggesting that at times there may be a chance in mean cell volume and therefore in the type of anemia with advancing age.

3. Serum Chemical Findings: The results of serum chemical determinations are detailed in table 1. Figures for total serum protein partition were normal in 10 of the 13 cases in which they were determined. In Cases VII, XV, and XXIII, total serum proteins were low.

TABLE 1. CLINICAL AND LABORATORY DATA ON 23 PATIENTS RE-EVALUATED

Case No	Series No.*	Name	Sex	Year of Birth	Age of Onset	Age 1st Admit.	Age Last Exam. (yr.)	Standard Deviations from Mean		Age Tests Performed (yr.)	Serum Protein (gm./100 cc.)	
								Wt.	Ht.		Albumin	Globulin
					Clinical Data							
I	—	M.F.	F	1936	6 yr.	9 yr.	13	−1.5	−3.3	13	4.6	2.2
II	—	P.M.	F	1937	5 mo.	7 yr.	13	−1.0	−1.0	10	5.9	2.8
III	(2)	M.K.	F	1937	10 mo.	1 yr.	12	−2.4	−2.2	11–12	4.3	2.8
IV	(12)	M.G.	F	1938	1 yr.	4 yr.	12	−2:0	−4.2	—	—	—
V	(3)	J.P.	F	1938	13 mo.	2 yr.	10	−1.4	−0.7	10	5.5	3.7
VI	(4)	M.N.	F	1939	Birth	4 mo.	11	−1.0	−2.6	11	—	—
VII	(6)	H.R.	M	1939	5 mo.	1 yr.	10	−1.4	−1.8	9–10	2.8	1.9
VIII	(18)	L.I.	F	1939	3 yr.	3 yr.	10	−1.7	−1.2	8–9	4.3	2.1
IX	(14)	R.T.	F	1940	Birth	2 yr.	9	−0.5	−1.4	6	4.9	2.3
X	—	P.F.	F	1941	10 mo.	2 yr.	9	−1.6	−0.7	8	5.3	2.9
XI	(30)	B.H.	F	1941	7 mo.	3 yr.	9	−0.5	+0.6	8	4.7	2.7
XII	(13)	A.S.	F	1941	7 mo.	10 mo.	9	−0.7	−1.3	9	—	—
XIII	(16)	M.M.	F	1941	6 wk.	1 yr.	9	−0.4	−0.6	7–9	4.5	3.6
XIV	(15)	R.F.	M	1941	5 mo.	10 mo.	9	−0.2	−0.8	9	4.7	3.1
XV	(22)	H.L.	F	1942	13 mo.	18 mo.	6	−0.9	−1.4	6	3.8	2.0
XVI	(26)	J.M.	F	1942	14 mo.	20 mo.	8	0.0	−1.0	8	—	—
XVII	(35)	C.R.	F	1943	6 mo.	2 yr.	7	−0.5	0.0	7	—	—
XVIII	(24)	J.M.	M	1943	5 mo.	1 yr.	7	−1.0	−1.0	5–7	—	—
XIX	(28)	J.M.	M	1943	Birth	16 mo.	7	0.0	+0.6	7	—	—
XX	(29)	M.A.	F	1943	12 mo.	14 mo.	7	−1.6	−1.2	5	—	—
XXI	(33)	V.G.	F	1943	15 mo.	18 mo.	6	−1.0	−0.9	5	—	—
XXII	(37)	W.M.	M	1943	11 mo.	16 mo.	7	+0.3	0.0	5–7	—	—
XXIII	(36)	M.R.	M	1944	2 wk.	11 mo.	5	0.0	−1.4	4	4.3	1.6

* Refers to the number assigned patients in the original series of 58 cases [3,4]

Serum calcium was within normal limits in all cases in which it was determined. Serum phosphorus was close to the upper limits of normal in almost all cases and in some instances it was definitely elevated. There was a slight increase in serum phosphatase levels in Cases X and XVIII.

4. Oral Glucose Tolerance Tests: In 18 patients, oral glucose tolerance tests were performed; the results are summarized in table 1. It will be noted that in four instances (Cases VIII, XVI, XVIII, XXII), fasting blood sugars were less than 60 mg./100 cc., an unexpected finding in patients in a good state of nutrition. The blood sugar curves rose normally by more than 40 mg., after ingestion of glucose, in all but four patients. In one of these (Case VII), the flat blood sugar curve was associated with an unsatisfactory clinical course, while Cases XXI and XXIII were among the youngest of the patients. No such explanation can be given for the low rise in Case XIV. It is equally difficult to explain the abnormally high rise in Case XXII.

SEVERAL YEARS AFTER ACUTE PHASE OF CELIAC DISEASE

Chemical Data									
Serum Calcium (mg./100 cc.)	Serum Phosphorus (mg./100 cc.)	Serum Phosphatase (B.U.)	Glucose Tolerance Test Blood Sugar (mg./100 cc. whole blood)		Serum Carotene (γ/100 cc.)	Vitamin A Absorption Test Serum Vitamin A (I.U./100 cc. serum)		Fecal Fat (average of 3-day stool collection)	
			Fasting	Maximal Rise Above Fasting Level		Fasting	Maximal Rise Above Fasting Level	Gm./24 hr.	Per Cent of Dry Weight
10.1	5.7	8.4	71	68	0	108	171	13.1	42
11.7	6.7	10.9	81	83	0†	58	70	5.4	24
11.4	4.9	5.2	80	67	5†	26	97	3.6	22
—	—	—	—	—	—	—	—	—	—
11.5	5.2	13.7	71	93	0	—	—	4.5	19
—	—	—	—	—	0	—	—	2.9	25
9.7	5.2	3.2	74	24	0†	62	72	15.0	26
11.2	7.0	14.0	49	98	5	—	—	5.6	23
—	—	—	101	62	92	—	—	2.5	20
—	5.6	15.0	78	86	126†	117	266	4.6	30
11.0	5.6	9.5	84	66	70	53	272	5.0	30
11.2	6.0	5.8	—	—	20	90	73	3.8	16
11.6	—	—	108	81	72	93	40	7.7	37
—	—	—	95	11	26	97	281	2.1	20
10.8	6.1	9.2	78	100	0	150	180	—	—
10.2	5.2	10.2	58	76	98	78	190	8.8	32
11.4	5.5	6.9	97	47	46	104	184	1.2	19
11.6	6.1	16.6	45	70	16	36	184	—	—
10.4	5.9	6.7	—	—	8	49	294	5.9	27
11.7	5.1	9.0	94	70	64	82	35	—	—
10.8	5.3	5.4	94	24	34	59	28	—	—
11.9	5.4	10.6	47	293	50	67	117	—	—
10.7	5.4	6.8	66	18	26	83	14	—	—

† Serum carotene and fecal fat determinations done at different times (from 3 mo. to 2 yr. apart).

5. Pancreatic Enzymes: Duodenal drainage for the assay of pancreatic trypsin and amylase was performed in all cases. In 18 patients, this test was carried out both on first and second admissions. The results are given in table 3 and chart 1. Pancreatic lipase was determined in most cases on the first admission and found to be normal; the test was not repeated on re-evaluation for reasons previously given.[3] Methods used and normal values have been discussed elsewhere.[3]

Pancreatic trypsin was normal in all instances. The variation in trypsin content between determinations in the same patient can be accounted for by variations in the dilution of the duodenal juice.

Three observations can be made about pancreatic amylase from the data charted in both table 3 and chart 1.

First, it can be readily seen that patients with celiac disease tend as a group to have low amylase values. Ninety-five per cent of celiac patients, both in the acute and latent phases,

TABLE 2A

HEMATOLOGIC DATA ON RE-EVALUATION

Case No.	Tests Performed		Red Cells (million/ cmm.)	Hgb. (gm./ 100 cc.)	Color Index	Volume of Packed Red Cells (cc./ 100 cc.)	Mean Corpuscular Volume (cmm.)	Mean Corpuscular Hgb. Concentration (per cent)	White Cells (thousand/ cmm.)
	Date	Age (yr.)							
I	1949	13	4.58	10.0	0.7	36	78	28	5.9
II	1948	10	3.62	12.0	1.2	41	113	29	9.0
III	1948	11	4.38	14.0	1.0	39	84	36	4.5
V	1947	10	4.70	12.0	1.1	42	89	31	4.7
VII	1949	10	4.02	12.0	1.0	40	99	30	11.2
VIII	1947	8	4.02	11.0	1.0	42	105	27	11.0
XII	1950	9	4.30	13.0	1.0	42	98	31	8.6
XIII	1947	7	5.00	10.0	0.7	46	92	21	12.5
XV	1948	6	3.24	12.0	1.3	50	154	24	8.5
XVIII	1948	5	5.50	13.0	0.8	43	78	30	9.8
XX	1948	5	4.00	10.5	0.9	39	97	27	11.1
XXI	1948	5	4.22	10.0	0.8	39	93	26	10.8
XXII	1950	7	4.28	13.8	1.1	41	96	34	—
XXIII	1948	4	4.06	12.0	1.0	42	104	29	11.2

had an amylase-trypsin ratio of less than 20%, while 77% of normal controls had an A/T ratio of more than 40%.

Second, it is evident that there is not much change in amylase as the patient passes from the acute to the latent phases of celiac disease. The absolute values for amylase vary on different determinations, because of varying dilution of the pancreatic juice, but the relation of amylase to trypsin appears to be fairly constant for the individual, regardless of his age, after the first few months of life.

Third, while reduction in pancreatic amylase is present in the great majority of cases of celiac disease, there are occasional patients with a high A/T ratio and some normal individuals with a low one.[3]

TABLE 2B

SERIAL BLOOD COUNTS ILLUSTRATING CHANGE IN MCV WITH ADVANCING AGE

Case No.	Tests Performed		Red Cells (million/ cmm.)	Hgb. (gm./ 100 cc.)	Color Index	Volume of Packed Red Cells (cc./ 100 cc.)	Mean Corpuscular Volume (cmm.)	Mean Corpuscular Hgb. Concentration (per cent)
	Date	Age (yr.)						
XV	12-22-43	2½	5.90	9.0	0.6	29	41	30
	12-28-43	—	5.30	7.8	0.7	29	55	27
	1-8-44	—	4.70	10.1	0.7	37	77	27
	1948	6	3.24	12.0	1.3	50	154	24
XXIII	1945	1	4.70	9.9	0.9	32	69	31
	1948	4	4.06	12.0	1.0	42	104	29

TABLE 3

PANCREATIC ENZYMES ON FIRST ADMISSION AND ON RE-EVALUATION IN PATIENTS WITH CELIAC DISEASE

Case No.	Yr. of Birth	Yr. Test Performed	Pancreatic Enzymes (viscosimetric u./cc.)		Amylase-Trypsin Ratio (per cent)	Yr. Test Performed	Pancreatic Enzymes (viscosimetric u./cc.)		Amylase-Trypsin Ratio (per cent)
			Trypsin	Amylase			Trypsin	Amylase	
I	1936	1945	410	55	13	1949	966	191	20
II	1937	1944	241	21	9	1948	141	10	7
III	1938	1938	255	48	19	1948	880	121	14
IV	1938	1942	388	190	49	—	—	—	—
V	1938	1939	150	40	27	1947	312	44	14
VI	1938	1939	100	—	—	—	—	—	—
VII	1939	—	—	—	—	1948	343	24	7
VIII	1939	1943	348	77	22	1947	773	46	6
IX	1940	1942	1039	106	10	1946	221	11	5
X	1941	1943	964	5	1	1949	959	100	10
XI	1941	1944	528	35	7	1948	726	77	11
XII	1941	1942	478	28	6	1950	607	339	56
XIII	1941	1942	424	3	1	1947	417	9	2
XIV	1941	1942	503	22	4	1950	195	24	12
XV	1942	1944	762	79	10	1948	314	39	12
XVI	1942	1944	428	0	0	1950	650	116	18
XVII	1943	1945	725	23	3	—	—	—	—
XVIII	1943	1944	242	34	14	1948	1050	237	23
XIX	1943	1944	411	58	14	1950	753	79	10
XX	1943	—	—	—	—	1948	258	29	11
XXI	1943	1945	832	69	8	1948	734	125	17
XXII	1943	1945	448	15	3	1948	802	99	12
XXIII	1944	1945	242	28	12	1948	670	57	9

6. Vitamin A Absorption Tests: In chart 2 the results of vitamin A absorption tests performed on patients in both the acute and latent stages of celiac disease are compared graphically. More detailed figures concerning the latter are found in table 1. Methods used and figures for normal controls have been discussed elsewhere.[3]

All normal controls showed a rise of more than 200 units above the fasting serum level of vitamin A after ingestion of a test dose of the vitamin. In contrast, 83% of celiac patients in the acute stage and 79% in the latent phase had a rise of less than 200 units; the majority less than 100 units and many less than 50 units. No great difference existed in the distribution of the rise in vitamin A curves between the acute and latent phases of celiac disease.

7. Serum Carotene Levels: Similar conclusions can be drawn from the determinations of serum carotene levels recorded in table 1 and chart 2. As in the case of the vitamin A tolerance tests, values for normal controls were obtained from figures published by other authors.[3]

Ninety-six per cent of normal controls over the age of one year had a fasting serum carotene level of more than 40 γ/100 cc., the average being 80 γ. In contrast, 90% of celiacs in the acute stage and 71% in the latent phase had serum carotene levels of less than 40 γ, most of them less than 10 γ/100 cc. Here again there is but little improvement over a period of years.

DUODENAL JUICE AMYLASE IN CELIAC DISEASE

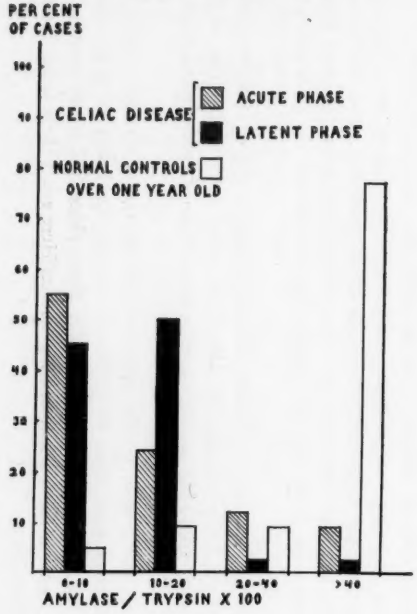

CHART 1

VITAMIN A ABSORPTION AND SERUM CAROTENE IN CELIAC DISEASE

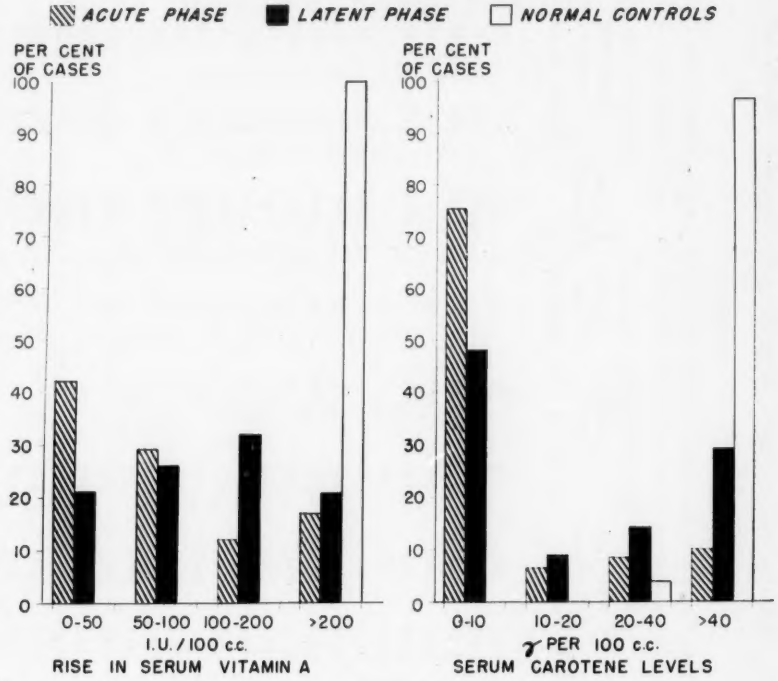

CHART 2

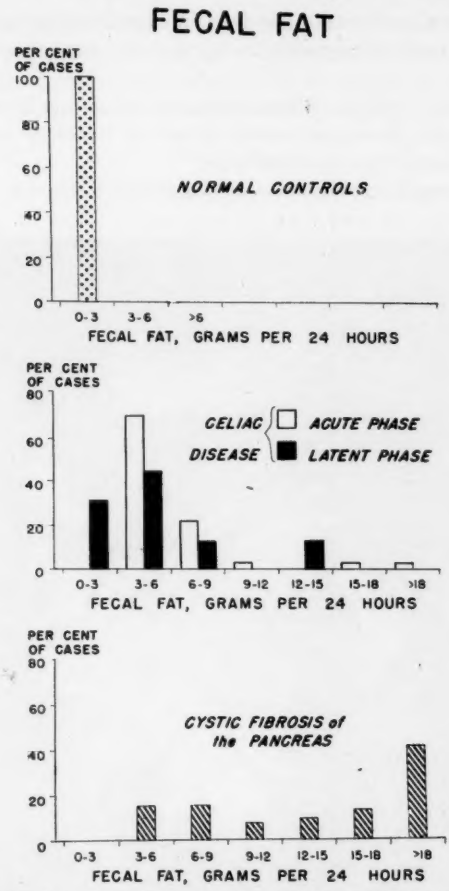

CHART 3. Daily fecal fat content (average of 3 day stool collection) in patients with celiac disease (45 cases), cystic fibrosis of pancreas (55 cases) and normal controls (42 cases). All patients were more than 6 mo. of age.

8. Fecal Fat: Fecal fat determinations in patients in the latent phase of celiac disease are given in table 1. In chart 3, the fecal fat content in the acute and latent phases of celiac disease is compared with that of normal controls and of patients with cystic fibrosis of the pancreas. The fecal fat was determined in all cases chemically by previously described methods.[5] All stools were collected for three days and values for fecal fat expressed in grams represent the average for 24 hours during this period. Three grams/24 hours were taken as the upper limit of normal.

It can be seen in chart 3 that all of the normal controls between the ages of 6 months and 12 years[5,6] had a fecal fat content of less than 3 gm./24 hours. In contrast, all patients in the acute phase of celiac disease and the majority of those in the latent phase had an increased amount of fecal fat. It may be inferred that many of the patients who seem to have made a complete clinical recovery from celiac disease still have an abnormal intestinal fat absorption as judged from fecal fat content.

It will also be noted from chart 3 that fecal fat excretion in celiac disease, while often greater than normal, rarely is comparable in degree to that seen in cases of cystic fibrosis of the pancreas.

9. Roentgenographic Findings: While osteoporosis of varying severity was observed in the acute phase of celiac disease, and skeletal maturation was often retarded, both of these features had largely disappeared on re-evaluation.

On re-evaluation, small intestinal motility was judged to be still abnormal in varying

FIG. 1. Transient intussusception in M. K. (Case III) on roentgenographic examination of small intestine.

degree in 17 of the 20 cases in which appropriate roentgenographic examination was performed. Frequently hypertonicity and hypermotility were present instead of hypotonia and hypomotility. Areas of transient segmental narrowing of unusual length were present in several instances. Excessive segmentation of the barium column, coarsening and obliteration of the mucosal folds, clumping and coarsely granular flocculation were present in varying degrees.

In 10 of 21 patients in whom 40 roentgenographic studies of small intestinal motility were made, findings interpreted as transient intussusceptions were seen either during the acute or latent stages of celiac disease or both. The changes were typical of ileo-ileal intussusception and were never present on the films taken one hour before or one hour later. One patient (Case III) was admitted to Babies Hospital at the age of 10 years with

the chief complaint of abdominal pain. No abnormality was found on physical examination, in an intravenous pyelogram, nor on roentgenographic visualization of the gallbladder, but on roentgenographic examination of the small intestine the patient was shown to have what was interpreted as a transient intussusception (Fig. 1).

Discussion

1. Mortality: Of the 58 patients with severe celiac disease previously listed,[3] three died. This mortality of 5% compares favorably with rates as high as 50% in patients observed prior to 1939.[1] The reason for the improvement in outlook in recent years has been mentioned elsewhere in this paper.

While in the group of cases under consideration there were no deaths during so-called "celiac crises," these episodes of sudden dehydration and acidosis remain the celiac patient's most critical danger. As previously pointed out,[3] a low total serum protein level is a warning signal, indicating severe illness and an unstable balance readily tipped by an intercurrent upper respiratory or other infection. Unless vigorous measures are undertaken immediately to restore the depleted fluid and electrolyte stores and bring the parenteral infection under control, death can ensue in a few hours.

Second only to the "crisis" as a menace to the life of the celiac patient is chronic failure to meet the caloric requirements leading to irreversible changes and death. This is well exemplified by the course in Cases 8 and 45 in whom repeated acute diarrheal episodes were treated by limitation of food, with fatal termination. Extended starvation in an effort to improve the character of the stools is therefore dangerous in these malnourished patients. It is also unnecessary as the stools of children with celiac disease do not return to normal for months or years after marked clinical improvement has taken place.

2. Improvement, "Latent Phase" and Ultimate Outlook: Unabated persistence of symptoms throughout childhood and into adult life, as described by Bennett, Hunter and Vaughan[7] and others, did not occur in the present series of cases nor indeed in any other patient observed in this hospital in the last 20 years. The only possible exception is a white male admitted recently for the first time at the age of 10 years with diarrhea, hypoproteinemia and hypocalcemia and with an onset of symptoms at the age of seven months. This is also the only case in which hypocalcemic tetany secondary to celiac disease has come under observation at Babies Hospital during the last two decades. The prominent deformities so commonly noted in the past[8, 9] as an end result of severe celiac disease have not been seen in this clinic during the same period.

At the present time and in this country, death or persistence of symptoms is therefore the exception, and improvement and clinical recovery from severe celiac disease, the rule. Better knowledge of dietary requirements and improved methods of dietary therapy are believed to be responsible for limiting the period of severe illness, so much shorter in the patients described than in the ones reported in former years from this country and elsewhere. In addition, setbacks in the patient's improvement are not as common or as severe as in the past because of effective control of intercurrent infections. The greatest clinical gains were made by the patients in the present series in the 6 to 24 months following initiation of treatment, the length of the "period of rapid improvement" being conditioned by the duration of symptoms prior to therapy.

Twenty-three patients were re-evaluated between the ages of 5 and 13 years, several years after the original admission, and it was found that despite remission of clinical symptoms, many abnormal laboratory findings persisted (termed "latent phase of celiac

disease"). In particular, intestinal fat absorption was still impaired in the great majority of cases as evidenced by failure of the serum vitamin A level to rise normally after ingestion of a test dose of the vitamin, by absent or low serum carotene and by excess fecal fat content (charts 2 and 3). On roentgenographic examination, small intestinal motility was still abnormal in varying degrees in all patients examined. Pancreatic amylase, reduced on first admission in almost all instances, was found not to have risen significantly except in one case, despite the passage of as long as 10 years.

From the clinical standpoint, these patients were all markedly improved and leading essentially normal lives. However, there was suggestive evidence of intolerance to dietary fat in 15 of 23 cases. Most of the patients followed had a moderate or normal intake of fat, and it is interesting in this respect to note that intolerance to dietary starch, which is such an outstanding and at times predominant symptom in young children with celiac disease, becomes much less marked after the age of 3 or 4 years. Conversely, impairment of fat absorption and intolerance to dietary fat plays an increasingly important role in the diagnosis and treatment of celiac disease in older children.

Many of these and similar patients will undoubtedly improve further with the passage of time. As to the ultimate outlook, however, the persistence of abnormal laboratory findings after years of clinical improvement or even apparent recovery supports the hypothesis that there is a basic constitutional physiologic or metabolic defect in celiac disease. It seems logical to expect that some of the patients who have had severe celiac disease in childhood may develop gastrointestinal disturbances in adult life.

It should be recalled in this respect that Hardwick in 1939[1] pointed out the existence in some cases of celiac disease of a "latent" period following which there may be a recrudescence of symptoms. Zellweger and Läuchli from Fanconi's clinic[2] made a study of 22 patients who had been admitted to their hospital for celiac disease several years previously, some as long as 30 years before, and found that intolerance to fatty foods, episodes of diarrhea and other clinical and laboratory abnormalities were still present in many.

3. Hematologic Findings: The finding of a macrocytic hypochromic anemia in four patients on re-evaluation runs counter to the accepted opinion of the peripheral blood findings in celiac patients. However, while it is the general experience that celiac patients in the acute stage have a microcytic hypochromic anemia, some evidence was presented suggesting that with the passage of time there may be a change from microcytic to a macrocytic blood picture.

The great variability in blood picture in this and similar conditions was remarked upon by Bennett, Hunter and Vaughan[7] who mentioned the frequent change in type of anemia following relapse or improvement. Cooke, Frazer and collaborators[10] also emphasized the change in hemoglobin content and in mean cell diameter in the same patient at different times. In the same paper these authors showed that a macrocytic hypochromic anemia was the commonest type in a group of adult or adolescent patients, in many of whom the disease had started in early childhood.

No conclusions, of course, can be drawn in view of the limited observations. It is clear, however, that this subject should be investigated further.

4. Roentgenologic Findings: The roentgenologic changes in small intestinal motility in the patients under consideration conformed with those which Golden[11] has grouped under the term "deficiency pattern." It was subsequently recognized by Golden[12] and others that these changes, although usually found in deficiency states such as celiac disease and

sprue, were by no means specific or diagnostic of these conditions. Similar patterns may be due to gastrointestinal allergy or fright and may even be found in apparently normal children.[13] However, in view of the persistence of abnormal laboratory findings in almost all patients in the present series, it is interesting and important to know that in all of them, small intestinal motility had not returned to normal even after years of clinical improvement.

Little can be said about the transient intussusceptions, which so many of the patients under investigation presented. It is a finding not recorded heretofore and its significance is not clear. It is not peculiar to celiac disease, but apparently common in this condition. Transient episodes of acute abdominal pain are not uncommon in these children and a relationship to the transient intussusceptions is suggested.

Finally a word should be said about the cause of osteoporosis. This was marked during the acute phase of celiac disease, but not present in the same patients on re-evaluation. In the past, osteoporosis has generally been attributed to lack of absorption of vitamin D, which when associated with arrest of growth was thought to give rise to rarefaction of the bones instead of rickets. When such patients were over the most severe phase of their illness and growth was restored, rachitic changes appeared.[9]

This sequence of events did not take place in the present series of cases. It seems probable that malnutrition and physical inactivity due to the patient's severe illness played a major role in production of osteoporosis. Albright and Reifenstein[14] have remarked on the relation between hypoproteinemia and osteoporosis, while Johnston[15] has recently re-emphasized the adverse effects of prolonged inactivity on both calcium and nitrogen balances.

The foregoing considerations apply primarily to patients who have developed in infancy or early childhood the full-blown picture of classic celiac disease. It is probable that the persistence of severe illness with associated chronic secondary nutritional changes over a period of months or years may aggravate a pre-existing metabolic or physiologic defect or even in some cases lead to irreversible changes. It is also probable that patients with a milder form of celiac disease who never experience the severe stage will go on in most instances to complete clinical and chemical recovery. Even in such cases, however, the basic constitutional metabolic defect would presumably persist and therefore the potential capacity for developing further difficulties would also remain.

Summary

The mortality and course of the illness of 58 patients with celiac disease, previously reported, are described. Three patients died; the remaining 55 went on to clinical recovery. The greatest clinical gains were made by these cases in the 6 to 24 months following initiation of treatment, but the abnormal character of the stools persisted for months or years. Relapses were not uncommon during the early years of improvement following upper respiratory infections or dietary indiscretions.

The results of the follow-up study of 23 patients, 3 to 11 years after the original admission to Babies Hospital, are reported. It was found that despite remission of clinical symptoms, many abnormal laboratory and roentgenographic findings persisted (termed "latent phase of celiac disease"). It is reasonable to expect that some patients who have had severe celiac disease during infancy or early childhood may experience a recurrence of gastrointestinal symptoms in adult life.

ACKNOWLEDGMENTS

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SPANISH ABSTRACT

Enfermedad Celiaca Idiopática

II. Evolución y Pronóstico

El mejor conocimiento de los requerimientos nutritivos, el control efectivo de las infecciones intercurrentes por medio de la quimioterapia y antibióticos y el mejoramiento de los métodos de terapéutica parenteral ha afectado en mucho la evolución de los enfermos celiacos. En este artículo se hace un análisis de un grupo de celiacos seguidos durante varios años, particularmente en la evolución, pronóstico y futuro de estos enfermos.

El estudio comprende 58 niños celiacos que previamente fueron reportados y la reevaluación clínica y de laboratorio de 20 de ellos, mas 3 nuevos casos, cuyas edades variaron entre 5 y 13 años en el momento de internarse al hospital para dicha reevaluación después de 3 a 11 años de su primera admisión.

De los 58 pacientes citados que tenían enfermedad celiaca severa, murieron 3 de ellos, uno por accidente transfusional, y los 2 restantes por fracaso continuo en administración calórica adecuada. En los 3 casos, no hubo respuesta a la terapeútica y tenían hipoproteinemia por largo tiempo antes de su muerte. Este porcentaje de mortalidad de 5% se compara muy favorablemente con la de 50% que se tenía antes de 1939 y las razones de dicha mejoría ya se citaron al principio.

Aun cuando no hubo muertes durante las llamadas "crisis celiacas," estos episodios de deshidratación súbita y acidosis siguen siendo el peligro más crítico del celiaco. El signo de alarma es la

hipoproteinemia, pues indica que el padecimiento es severo y que existe un equilibrio inestable que facilmente se rompe con motivo de una infección y a menos que se haga una terapeútica de hidratación y electrolítos inmediata y se controle la infección, la muerte sobreviene en unas cuantas horas.

La segunda amenaza mortal del celiaco es la imposibilidad de administrarle sus requerimientos calóricos que lleva a cambios irreversibles. Los períodos de hambre prolongados después de episodios diarreicos agudos y repetidos deben evitarse en estos enfermos desnutridos ya que no son necesarios para tratar de mejorar el carácter de las evacuaciones pues estas no se hacen normales sino después de meses o años cuando la mejoría clínica ya es muy marcada.

Los 55 enfermos que sobrevivieron fueron mejorando y finalmente se recuperaron clínicamente siguiendo un patron similar pero con grandes variaciones en la duración de cada fase. La mejoría después de la iniciación de la dietoterapia fué rápida y se caracterizó por aumento marcado en el peso, apetito voraz y retorno a lo normal de algunas pruebas de laboratorio, pero las evacuaciones anormales persistieron en general y hubo que continuarse estrictamente la dieta. Este "periodo de mejoría rapida" varió entre 6 meses y 2 años y se prolongaba en razón directa a la duración de los síntomas previa a la terapéutica. Después de este período, la mejoría continuó lentamente por meses o años, terminando en la remisión completa o casi completa de los síntomas clínicos en la mayoría de los casos. El aumento de peso decreció y el apetito retornó a lo normal.

Las evacuaciones mejoraron gradualmente, pero eran frecuentes los brotes de diarrea con evacuaciones típicas de la enfermedad celiaca después de infecciones respiratorias superiores ó de episodios de disgresiones dietéticas.

La persistencia de los síntomas del celiaco durante toda su infancia y aun en su vida adulta que ha sido reportada por varios autores, no se verificó en este grupo de celiacos, con excepción de un solo caso en que hubo también hipoproteinemia e hipocalcemia con tetania. Tampoco se vieron deformidades óseas marcadas como frecuentemente se observaban en epocas pasadas. La muerte o la persistencia de los síntomas es por consiguiente la excepción y la mejoría y curación clínica de los casos severos, es la regla. El mejor conocimiento de los requerimientos dietéticos y de la dietoterapia son los factores responsables en la actualidad del acortamiento del período severo o grave de la enfermedad y los retrocesos en la mejoría de los enfermos no son ni tan comunes ni tan frecuentes como previamente al control efectivo de las infecciones intercurrentes por medio de la químico y antibioterapia.

En el grupo de 23 enfermos que se admitieron al hospital para su reevaluación total varios años después de su primera admisión, se encontró que a pesar de la remisión de los síntomas clínicos, persistían anormales muchas pruebas de laboratorio en particular la disminución de la absorción de las grasas, en la mayoría de ellos, evidenciada por imposibilidad de subir el nivel de la vitamina A en el suero como normalmente se logra después de la administración de cierta cantidad de ella; ausencia o baja cantidad de caroteno del suero y exceso de grasa fecal. Asímismo, persistencia de la motilidad anormal del intestino delgado de grado variable en todos los enfermos y además, persistencia de la reducción de la amilasa pancréatica tal como se encontró en la admisión inicial en casi todos los casos.

Desde el punto de vista clínico los enfermos estaban muy mejorados y vivían una vida en esencia normal, sin embargo, había intolerancia evidente a las grasas en 15 de los 23 enfermos. La mayor parte tenían una ingesta moderada o normal de grasas y es interesante el hecho de que la intolerancia a los feculentos que es marcada y aún predominante en los celiacos pequeños mejora notablemente después de los 3 ó 4 años de edad, contrariamente a lo que sucede con la absorción de las grasas cuyo déficit tiene una significación muy importante en el diagnóstico y tratamiento de la enfermedad celiaca en niños mayores.

En cuanto al futoro de los enfermos a mayores edades, es indudable que aun mejoren más al pasar del tiempo pero por la comprobación definitiva de la persistencia de datos de laboratorio anormales después de años de mejoría clínica y aún de curación aparente, lo cual respalda la hipótesis de que existe un defecto básico constitucional ya sea fisiológico o metabólico en esta enfermedad, es lógico esperar que algunos de estos enfermos que han tenido un padecimiento intenso desarrollen trastornos gastrointestinales durante su edad adulta.

De hecho Hardwick señaló en 1939 la existencia de un período "latente" en algunos celiacos a continuación del cual puede presentarse recrudescencia de los síntomas y otros autores también han encontrado intolerancia a los alimentos grasosos, episodios diarreicos y otras anormalidades clínicas y de laboratorio en celiacos, aún hasta 30 años después de iniciarse la enfermedad.

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INCIDENCE OF GROSS VISUAL DEFECTS DUE TO RETROLENTAL FIBROPLASIA

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GROSS visual handicap as a result of retrolental fibroplasia among premature infants has excited increasing interest in the decade since Terry's initial report in 1942.[1] Knowledge of the pathogenesis of the condition has been greatly extended following the observations of Owens and Owens,[2] Reese and Blodi,[3] Laupus and Bousquet.[4] There are reports of visual defects due to retrolental fibroplasia seen in selected groups, such as infants born in individual hospitals and medical centers.[5] The number of cases has appeared to increase in some hospitals in the past few years,[6] whereas there has been an apparent sudden decrease in others. The frequency of the condition also has seemed to vary markedly within limited geographic areas.

This report presents the results of a study of the incidence of gross visual defects due to retrolental fibroplasia among infants born during 1948 and 1949 to residents of New York State, exclusive of New York City. It was hoped that two years of data would provide a large enough number for study of some of the possible factors related to the development of retrolental fibroplasia as well as the establishment of a reasonably reliable baseline for comparison with future studies in New York State and elsewhere.

Laupus and Bosquet[4] have described six stages in the pathogenesis of retrolental fibroplasia, starting with arterial and venous tortuosity of the retinal vessels, followed by preretinal and subhyaloid hemorrhages, extending later into the vitreous, with the formation of fibrous bands and neovascularization. The fifth stage is that of retinal detachment. In the sixth and fully developed stage of retrolental fibroplasia, retrolental membranes are formed by fusion of the peripheral folds of detached retina and adherence of the detached retina to the posterior surface of the lens. Laupus and Bousquet also point to the potential reversibility of the disease at any point short of severe retinal detachment.

The chief burden to the families and communities concerned from retrolental fibroplasia is the partial or complete bilateral blindness in irreversible advanced cases. Except for two cases of unilateral blindness, the present study is limited to cases with such gross impairment in vision, corresponding in general to stages 5 and 6 described by Laupus and Bousquet. Special emphasis is placed on this point to avoid confusion which would result from comparing the incidence rates presented in this paper with the incidence rates of all stages of retrolental fibroplasia in other publications.

METHOD OF STUDY

Since it was not feasible to study the nearly 300,000 infants born to residents of upstate New York in 1948 and 1949, only those infants whose birth certificates indicated birth weights of less than

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2000 gm. (or whose birth weight was estimated to be less than 2000 gm. based on length of gestation when birth weight was not stated) were selected for study. This selection was made on the basis of previous reports suggesting that this group might be expected to be the most productive.

Because of the possibility that the condition being studied might not be noticed in the early stages of infancy, the birth certificates were matched with the death certificates and the study further limited to those found to have survived to 4 mo. of age.

Questionnaires were then sent by mail to the mothers of the selected infants at the addresses recorded on the birth certificates. The questionnaire included the following 3 simple questions:

1. Has he (or she) had any long or serious illness?
2. Does he (or she) have any trouble in seeing?
3. Does he (or she) have any trouble in hearing?

Provision was made on the questionnaire for checking "yes" and "no" answers, entering the name of the infant's physician and a description of any illness or physical defect in the infant. A short letter requesting the co-operation of the parents in a study of the health and care of "small" infants, as well as a self-addressed stamped envelope, were enclosed with each questionnaire.

A follow-up letter was sent to parents who did not reply to the first inquiry; a second follow-up letter was mailed to those not responding to the 1st 2 inquiries. If no questionnaire was returned by mail, the public health nurse in the area was asked to make a home visit to obtain the desired information. Public health nursing visits were requested in preference to the impersonal approach by mail in the event of death of the infant after 4 mo. of age, death of the mother or a twin, or a suggestion that the infant was born out of wedlock. The Commission for the Blind and the Bureau of Child Welfare, both of the New York State Department of Social Welfare, assisted in locating children who had been adopted or placed in foster homes or whose families had moved from the addresses reported on the birth certificates. One child blind from retrolental fibroplasia was finally located in North Dakota, and his medical report was obtained from an ophthalmologist in Minnesota.

When there was any indication of visual difficulty from information on the questionnaire or home visit, other than that related to an obvious strabismus or similar condition, a letter was sent to the physician named on the questionnaire or to the State Commission for the Blind, requesting more exact information. A copy of an editorial in the *New York State Journal of Medicine*[7] was enclosed with each letter to a physician. In this editorial the Medical Society of the State of New York endorsed the study and urged physicians to provide any information needed for its completion. When a clearcut diagnosis of the cause of the gross visual defect was not obtained in the reply from a physician, several steps were taken to obtain an ophthalmologic report. Ophthalmologists mentioned by family physicians were queried directly. In many of the other cases detailed ophthalmologic reports were secured from the State Commission for the Blind.

Validity of Results

Of the 296,430 resident live births in New York State, exclusive of New York City, in 1948 and 1949, 3667 or 1.2% weighed less than 2000 gm. at birth and survived to 4 months of age. Replies were received for 3377, or 92%. Approximately 85% of the replies were mail questionnaires; the remaining 15% were public-health-nursing reports.

Since public-health-nursing follow-up was done for those who failed to reply to the mail questionnaire, the 290 infants for whom information is lacking are those who could not be located through the usual public-health-nursing technics. This group is heavily weighted with infants whose birth certificates show the name of the father as "unknown." It seems reasonable, however, to assume that there is little if any bias in the study as a result of the loss of this group.

It is believed that the unusually large proportion of replies to the mail questionnaire probably is due not only to the relatively high degree of literacy in New York State but also to the fact that the problem under study was one of great concern to the parents. The experience of others in receiving inaccurate information through the use of mail questionnaires immediately suggests the question of the reliability of the answers received

TABLE 1

COMPARISON OF REPLIES BY PARENTS AND PUBLIC HEALTH NURSES TO QUESTION ON "TROUBLE IN SEEING"

Answer by parent	Answer by public health nurse	No.	Per cent
Total checked		131	100.0
Yes	Yes	25	19.1
No	No	90	68.7
Yes	No	14	10.7
No	Yes	2	1.5

in this study. In order to study this factor the public-health nurses made home visits to a randomly selected sample of 131 of the children born in 1948 and included in the study. The comparison of the answers made by the mothers and the public-health nurses is shown in table 1. There was agreement in 115 or 88% of the cases. Such disagreement as did occur is due to the tendency on the part of the parent to report transient ocular imbalance and similar minor conditions as "trouble in seeing." There were only two instances of failure on the part of the parent to report conditions reported by the public-health nurse. Both of these were cases of strabismus, one of which developed after the parent had

TABLE 2

INCIDENCE OF GROSS VISUAL DEFECTS DUE TO RETROLENTAL FIBROPLASIA BY BIRTHWEIGHT

Resident Births Surviving to 4 Months of Age
New York State (Exclusive of New York City)
1948 and 1949

Year of birth and birthweight* (gm.)	No. of replies	Cases†	
		No.	Per cent
1948 and 1949			
Total	3377	50	1.5
Less than 1000	44	7	15.9
1000 to 1499	562	24	4.3
1500 to 1999	2771	19	0.7
1948			
Total	1620	27	1.7
Less than 1000	25	5	20.0
1000 to 1499	276	13	4.7
1500 to 1999	1319	9	0.7
1949			
Total	1757	23	1.3
Less than 1000	19	2	10.5
1000 to 1499	286	11	3.8
1500 to 1999	1452	10	0.7

* Unknown birthweights (approximately 7%) were estimated and distributed in groups on basis of gestation.

† Gross visual defects due to retrolental fibroplasia.

returned the completed questionnaire. This would seem to indicate that no serious visual impairment due to retrolental fibroplasia would be likely to be missed through failure of the parent to answer "yes" to the question on vision. In many instances the answers checked were supplemented by lengthy letters pointing to continued concern for the child's health or displaying justifiable pride in the job of raising a delicate infant.

Results of Study

A total of 50 cases with gross visual defect due to retrolental fibroplasia was reported in the infants about whom information was obtained, or an over-all incidence rate of 1.5% (table 2). The rates of 1.7 and 1.3% for the two years, 1948 and 1949, respectively, are not significantly different.

Birth Weight: The relationship of the incidence rate to birth weight was clearcut (table 2). The incidence rates decreased from 15.9% in the birth weight group under 1000 grams to 4.3% and 0.7% in the two successively higher birth weight groups.

TABLE 3

Incidence of Gross Visual Defects Due to Retrolental Fibroplasia, by Length of Gestation

Resident Births Surviving to 4 Months of Age
New York State (Exclusive of New York City)
1948 and 1949

Length of gestation*	No. of replies	Cases†	
		No.	Per cent
Total	3377	50	1.5
Under 7 mo.	288	22	7.6
7 mo.	1184	23	1.9
8 mo. and over	1898	5	0.3
Not stated	7	0	0.0

* Gestation in weeks reported in 1949 converted to months as follows:
Under 29 wk. = under 7 mo.
29 to 32 wk. = 7 mo.
33 wk. and over = 8 mo. and over.

† Gross visual defects due to retrolental fibroplasia.

Period of Gestation: The incidence of gross visual defects due to retrolental fibroplasia was analyzed by the infant's period of gestation as given on the birth certificate (table 3). The infants reported to have the shortest periods of gestation were found to have the highest incidence, the rate in the group of 288 infants with a period of gestation under 7 months being 7.6% as compared with a rate of 0.3% in the group of 1898 infants whose gestation period was reported as 8 months or more.

Birth Weight and Period of Gestation: The relationship of the combined factors of birth weight and gestation to the incidence of gross visual defects due to retrolental fibroplasia is presented in table 4. Although the numbers are small and the measure of gestation as reported on the birth certificate is subject to question, it is of interest to note that within each birth weight group, the incidence of the condition was found to be inversely related to the length of gestation. In the 1000-1499 gm.-birth-weight group, for example, an incidence rate of 7.0% was found among the infants whose period of gesta-

TABLE 4

INCIDENCE OF GROSS VISUAL DEFECTS DUE TO RETROLENTAL FIBROPLASIA BY BIRTHWEIGHT AND LENGTH OF GESTATION

Resident Births Surviving to 4 Months of Age
New York State (Exclusive of New York City)
1948 and 1949

Birthweight*	Length of Gestation†		
	Under 7 mo.	7 mo.	8 mo. and over
No. of replies			
Less than 1000 gm.	21	17	6
1000–1499 gm.	143	262	156
1500–1999 gm.	124	905	1736
Cases‡			
Less than 1000 gm.	6	1	0
1000–1499 gm.	10	11	3
1500–1999 gm.	6	11	2
Per cent			
Less than 1000 gm.	28.6	5.9	0.0
1000–1499 gm.	7.0	4.2	1.9
1500–1999 gm.	4.8	1.2	0.1

* Unknown birthweights (approximately 7%) were estimated and distributed in groups on the basis of gestation.

† Exclusive of seven children in which gestation is unknown.

‡ Gross visual defects due to retrolental fibroplasia.

tion was recorded as less than 7 months, as contrasted with a rate of 1.9% among those 8 months or more. This observation is in line with recent studies of Steiner and Pomerance[8] which demonstrated the higher fatality rates among premature infants of a given birth weight when the period of gestation was shorter.

Complications of Pregnancy: Complications* of pregnancy are reported as supplemental medical information on the reverse of the birth certificate in New York State. The reporting of complications on the birth certificate made it possible to investigate this factor,

* Complications, for the purposes of this study, include the following:

Bleeding during pregnancy (threatened abortion)
Pelvic tumors
Placenta praevia
Eclampsia
All other toxemias
Accident (and overexertion)
Appendicitis
Chronic nephritis
Other diseases or malformations of genitourinary system
Tuberculosis
Diseases of endocrine glands
Diseases of heart
All respiratory (pneumonia, influenza, bronchitis, etc.)
Syphilis
Hypertension (alone)
Diabetes
Pyelitis and other infections, incidental to pregnancy
Anemia and other blood diseases
Other intercurrent diseases (including chronic respiratory)

although the number is too small to attempt a breakdown by type of complications. Previous studies have suggested that the hazard of gross visual handicap due to retrolental fibroplasia is related to complications occurring during the mother's pregnancy.

The incidence of gross visual defects due to retrolental fibroplasia, adjusted* for differences in the weight distribution, was 1.8% in the group of 541 infants for whom one or more of the conditions included in the authors' definition of complications were reported. The adjusted rate in the group of 2532 infants for whom it was stated that there were no complications was 1.4%. The difference in these two rates is not statistically significant.

The birth certificates of infants who developed gross visual defects due to retrolental fibroplasia contained a distribution of major complications of pregnancy comparable to the entire group for which complications were reported.

TABLE 5

INCIDENCE OF GROSS VISUAL DEFECTS DUE TO RETROLENTAL FIBROPLASIA BY BIRTHWEIGHT* AND PLACE OF RESIDENCE

Resident Births Surviving to 4 Months of Age
New York State (Exclusive of New York City)
1948 and 1949

Place of residence (Region)	Less than 1500 gm.			1500 to 1999 gm.		
	No. replies	Cases†		No. replies	Cases†	
		No.	Per cent		No.	Per cent
Total	606	31	5.1	2771	19	0.7
Buffalo	125	13	10.4	585	5	0.9
Rochester	83	7	8.4	436	3	0.7
Syracuse	135	5	3.7	590	3	0.5
Albany	103	2	1.9	444	3	0.7
White Plains	160	4	2.5	716	5	0.7

* Unknown birthweights (approximately 7%) were estimated and distributed in groups on basis of gestation.

† Children with gross visual defects due to retrolental fibroplasia.

Geographic Variation: There appears to be a statistically significant variation in the incidence of gross visual defects due to retrolental fibroplasia, ranging from 2.5% in the Buffalo region in the westernmost part of the state and gradually decreasing to 0.9 and 1.0% in the Albany and White Plains regions, respectively, in the eastern part of the state. This trend is due entirely, however, to the geographic differences in incidence in the birth weight group under 1500 gm. The distribution of the cases by region is shown in table 5. Although this trend is statistically significant,† and is observed among

* Adjusted for differences in weight distribution, using all children included in the study as the standard population.

† The probability of a chance difference as large as that observed between the Buffalo and White Plains Regions in the weight group under 1500 gm. is .005.

births in both large and small hospitals, its meaning is obscure. Further studies of the consistency of this trend probably are indicated.

Other Factors: The incidence rate, adjusted for differences in weight distribution, was found to be slightly higher in males than in females, 1.7% to 1.2%. Although not statistically significant, this slight difference is in the same direction as in other reports. The rates among single and multiple births were found to be similar when adjusted for birth weight.

Variation in incidence by month of birth was also studied. The number of infants born in any one month was too small to permit any conclusions, but there was no consistent aggregation of cases in any month or in any season of the year. This is in accord with the study by Speert, Blodi and Reese.[9]

The relationship of the age of mother to the incidence of gross visual defects due to retrolental fibroplasia in their offspring was also investigated. The weight-adjusted rate among the 2198 infants born to mothers under 30 years of age was 1.3% which is not significantly different from the rate of 1.9% among the 1179 infants born to mothers 30 years of age or more. The number of infants under study was too small to permit analysis of other factors, such as parity of mother, which might have a bearing on this relationship.

Summary and Conclusions

A study was made of the incidence of gross visual impairment due to retrolental fibroplasia among infants born to residents of New York State, exclusive of New York City, in 1948 and 1949, whose birth certificates indicated birth weights of less than 2000 gm. and who survived to the age of 4 months. Information was obtained regarding 3377 infants or 92.1% of the 3667 in the group described.

A total of 50 cases with gross visual defects due to retrolental fibroplasia, or an over-all incidence rate of 1.5%, was found. The incidence rates decreased from 15.9% in the birth weight group under 1000 gm. to 4.3% in 1000-1499 gm. group, and 0.7% in the 1500 to 1999 gm. group. The infants reported to have the shortest period of gestation were found to have the highest incidence, the rate in the group with a period of gestation under seven months being 7.6% as compared with a rate of 0.3% in the group whose gestation period was reported as eight months or more.

Although the numbers are small and the measure of gestation as reported on the birth certificate is open to question, the incidence of the condition within each birth weight group was found to be inversely related to the length of gestation. In the 1000-1499 gm. birth weight group, for example, an incidence rate of 7.0% was found among the infants with recorded periods of gestation of less than seven months, as contrasted with a rate of 1.9% among those eight months or more.

There was no statistical difference in the incidence of the condition in the group of infants for whom one or more major complications of the mother's pregnancy was reported when compared with the group of infants on whose birth certificates the statement appeared that no such complication occurred. Among infants weighing less than 1500 gm. at birth, a statistically significant variation in the incidence of the condition was found in different regions of the State. The incidence rate, adjusted for differences in weight distribution was found to be 1.7% in males and 1.2% in females. The incidence rate among infants born to mothers under 30 years of age was 1.3%, which is not significantly different from the rate of 1.9% among the infants born to mothers 30 years of age or more.

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SPANISH ABSTRACT

Incidencia de los Defectos Visuales Gruesos Debidos a la Fibroplasia Retrolental

Este informe representa los resultados de un estudio acerca de la incidencia de los defectos visuales obvios o gruesos debidos a la fibroplasia retrolental en los niños nacidos de residentes del estado de Nueva York, exclusivamente de la ciudad de Nueva York durante los años de 1948 y 1949, cuyos certificados de nacimiento indicaron pesos al nacer de menos de 2000 gramos y que vivieron como mínimo hasta 4 meses. Fueron 3667 niños en total los que cayeron dentro de este grupo y de ellos se obtuvo información en 3377 o sea el 92.1%.

Se encontró un total de 50 casos de entre esos 3377 niños, que presentaban defectos visuales toscos, o sea una incidencia de 1.5%. La incidencia decreció de 15.9% correspondiente al grupo cuyo peso al nacer era menor de 1000 gramos, a 4.3% que correspondió al grupo que pesó entre 1000 y 1499 gramos y a 0.7% en el grupo entre 1500 y 1999 gramos. La mayor frecuencia se encontró también en los niños que nacieron de los embarazos más cortos pues el índice en el grupo con embarazo menor de 7 meses fué de 7.6% en comparación con 0.3% que se obtuvo en aquellos cuya duración fué de 8 meses o más.

Aunque los números son pequeños y la duración del embarazo como se reporta en el certificado de nacimiento se presta a la duda, la incidencia de los trastornos visuales dentro de cada grupo de pesos del nacimiento fué inversamente proporcional a la duración del embarazo. Por ejemplo, en el grupo de pesos al nacimiento de 1000 a 1499 gramos, una incidencia de 7.0% se encontró entre los niños nacidos de embarazos de menos de 7 meses, en contraste con la encontrada en los nacidos de embarazos de 8 meses o más, que fué de 1.9%.

No hubo diferencia estadística al comparar la incidencia de estos defectos en el grupo de niños en cuyas madres se reportaron una o más complicaciones importantes del embarazo con el grupo en que, de acuerdo con el certificado de nacimiento también, no presentaron ninguna. Entre los lactantes con peso al nacer menor de 1500 gramos se encontró una variación estadísticamente significante en la frecuencia de estos trastornos en las distintas regiones del Estado de Nueva York.

El índice de frecuencia, previamente ajustado a las diferencias de distribución por peso, fué de 1.7% en niños y de 1.2% en niñas. El índice de frecuencia entre los niños nacidos de madres de menos de 30 años de edad fué de 1.3%, que no es diferente en forma significante del hallado entre los nacidos de madres de 30 años de edad o más y que fué de 1.9%.

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DOMINANT INHERITANCE OF DIABETES INSIPIDUS

A Family Study

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INTRODUCTION

THIS report deals with a family of "drinkers," in which the affected members suffer from diabetes insipidus, a disease which appears in the family so frequently that they recognize it as a family characteristic. The present paper will deal mainly with the clinical aspects of the study. A detailed presentation of the genetic data will be published elsewhere.

Definition: Diabetes insipidus is a rare chronic condition characterized by an increased thirst and the passage of large quantities of urine of low specific gravity. It is due to a deficiency of pitressin, a hormone produced by the posterior lobe of the pituitary gland which regulates the water metabolism of the body, or to an irresponsiveness of the kidney to this hormone.[1]

Physiology: About two -thirds of the 180 l. of water filtered through a normal kidney in 24 hours is reabsorbed in the proximal convoluted tubules. Distal to this, most of the remaining water is reabsorbed.[2] Pitressin is thought to exert its antidiuretic effect by influencing the water-reabsorbing activity of the loop of Henle.[3]

The production of pitressin depends on a complex functional unit, which consists of the posterior lobe of the pituitary gland, part of the infundibular stalk, the nucleus paraventricularis and the nucleus supraopticus of the hypothalamus, and the nerve tracts connecting them. Damage to any part of this functional unit may cause a deficiency in the excretion of pitressin, and diabetes insipidus may be expected to develop, provided the anterior pituitary and thyroid glands are intact.[2]

Classification: The causes of diabetes insipidus may be classified as follows:

A. Due to a deficiency in pitressin.
   1. Primary, due to a defect inherent in the gland itself.
      a. Hereditary.*
      b. Sporadic. These may actually be hereditary but cannot be proved so in the absence of a positive family history.
   2. Secondary, due to destruction of the diencephalic-hypophyseal system by trauma, infection (encephalitis, tuberculosis or syphilis), tumors, xanthomatosis or vascular accident.

B. "Nephrogenic" diabetes insipidus, due to a defect in the kidney tubules, which interferes with water reabsorption.

Symptomatology: The symptomatology of diabetes insipidus has been described in

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* The authors take exception to the practice of classifying the hereditary type as "idiopathic."

reviews by Warkany and Mitchell[4] and by Forssman[5] and will be discussed only briefly here. The outstanding symptoms are polydipsia and polyuria, the volume of fluid ingested and excreted varying from 4 to 35 quarts daily. The urinary specific gravity is very low. Symptoms have been said to decrease with fever and increase with exercise. Restriction of fluids causes various complaints including headache, fatigue, muscular pain, hypothermia and tachycardia.

Differential diagnosis: Diabetes insipidus must be distinguished from several other conditions showing polydipsia and polyuria, including diabetes mellitus, chronic nephritis, Addisonian crises occurring in young infants, and psychogenic polydipsia. The latter is difficult to distinguish clinically from true diabetes insipidus, but can be differentiated by observing the effect of an intravenous injection of hypertonic saline solution on urine flow. In normal individuals and those with psychogenic polydipsia there is a marked decrease in urinary flow, but in patients with true diabetes insipidus there is no response.[6] This test was performed on Cases 1 and 2 described below, where it clearly ruled out a psychogenic basis for their disease.

Once the diagnosis of diabetes insipidus is established, the pitressin-deficient type must be distinguished from the nephrogenic type. The latter condition is resistant to pitressin, since the defect is in the kidney tubule rather than in the production of pitressin, and shows a sex-linked recessive pattern of inheritance.[7,8]

Presentation of Cases

Case 1. The proband,* V-12, a 9 yr. old girl, was admitted to hospital as a case of suspected rheumatic fever, with a 4 yr. history of intermittent joint pains associated with bouts of fever, lasting 7 to 10 days. It was noted in the functional inquiry that she had "always" had polydipsia and polyuria, voiding 10 to 12 times a day and having to get up 2 to 3 times a night to have a drink and urinate. This observation, confirmed on the ward and supported by the demonstration of a low urinary specific gravity, suggested to one of the authors (C.B.P.) a diagnosis of diabetes insipidus. A review of the family history confirmed this impression, since there were a large number of relatives, including the mother, who were "water-drinkers" (see section C below).

Birth and past history had been uneventful except for existence of polyuria and polydipsia since infancy. Physical examination revealed a thin, intelligent girl, who presented normal physical findings. Analysis of urine yielded normal findings except for a specific gravity of 1.001. Daily fluid intake, when no tests were being done, varied from 1120 to 3900 cc. and daily output from 840 to 4200 cc. Several urine concentration tests were done, where fluids were restricted for 24 hr.; all urine specimens had a specific gravity of less than 1.004 except for one overnight specimen in which it was 1.010. Patient's temperature reached 37.7°C. on 2 occasions during stay in hospital, but there was no apparent relation between her febrile episodes and her water balance. A thorough hematologic and biochemical examination, including liver function tests, was normal. ECG was within normal limits. Chest and skull RG showed normal findings. In particular cardiac diameter was not enlarged and sella turcica appeared normal.

During her stay in hospital it became evident that she did not have rheumatic fever, and attention was therefore directed mainly towards finding a cause for the polydipsia and polyuria. Urine of consistently low specific gravity with other normal findings, and characteristic family history argued strongly in favor of hereditary diabetes insipidus as a basis for her defective water balance.

To rule out a psychogenic basis for the polydipsia and polyuria the following test[6] was done. Patient was deprived of water for 8 hr. and then given 20 cc. of water/kg. body weight over a period of 1 hr. Average rate of urine flow during this hour, measured by withdrawing samples at regular intervals through a retention catheter, was found to be 5 cc./min. A 3% solution of sodium chloride was then given intravenously at a rate of 0.25 cc./kg. body weight/min. for 45 min. During this time urinary specific gravity did not rise above 1.006 and rate of urine flow did not fall (in psychogenic polydipsia a marked fall in rate of flow is expected in the 1st 15 min.). As a con-

* The individual who first brought the family to the authors' attention.

firmatory test an injection of 1 pressor u. of aqueous pitressin was given intravenously, and the rate of urine flow dropped to 2 cc./min. with a rapid rise in specific gravity to 1.017. Several days later patient was given pitressin tannate 1.25 pressor u. in oil, following which specific gravity of urine rose from 1.002 to 1.019 and rate of production was markedly decreased for 24 hr. She had no excessive thirst, and for the first time in her life she did not have to get up at night to have a drink or pass urine.

Case 2. V-3, a 10 yr. old female cousin of proband, was stated by proband's mother to be a severely affected "drinker" and was consequently admitted for investigation of polydipsia and polyuria. She was otherwise perfectly well. Excessive intake and excretion of water had first been noted at about the age of 2 yr. and had been present ever since. She was said to urinate 6 to 8 times a day and 2 to 3 times a night. Birth history and subsequent development had been normal. Examination revealed a plump, intelligent female child with no abnormal physical, hematologic, biochemical or radiologic findings.

During stay in hospital the patient's usual fluid intake and output was about 2000 cc. daily. Specific gravity of urine varied from 1.001 to 1.005. A 24 hr. concentration test elevated specific gravity to 1.012. Intravenous injection of hypertonic saline had no effect on rate of urine flow or its specific gravity while an intravenous dose of aqueous pitressin 1 pressor u. decreased urine flow from 9.2 to 3.9 cc./min. and elevated specific gravity to 1.013. On 3 occasions during 7 day admission temperature reached 37.7°C. for no apparent cause, and as with Case 1, there was no apparent relation between fever and water balance. Prior to discharge from hospital patient was given pitressin tannate 1.5 pressor u. in oil. This raised urinary specific gravity to 1.019 and caused a marked decrease in fluid intake and output, which lasted 48 hr.

Family Data

Information of varying degrees of accuracy has been obtained concerning 137 members of the family, in six generations (Fig. 1). Of these, 41 have been classified as cases of diabetes insipidus. Eleven of the affected individuals have been demonstrated to have polyuria and a low urinary specific gravity without glycosuria either through direct examination by the authors or from hospital records. Of these, 5 have had injections of pitressin, followed by a temporary rise in urinary specific gravity. The other individuals listed as affected have been so classified on the basis of information received from informants who were closely related to and personally acquainted with the person in question. The present paper will deal with the relevant details of only those family members affected with diabetes insipidus.

Generations I and II: Little information was available about the members of the first two generations represented in the pedigree. I-1, who married twice, had the maiden-name

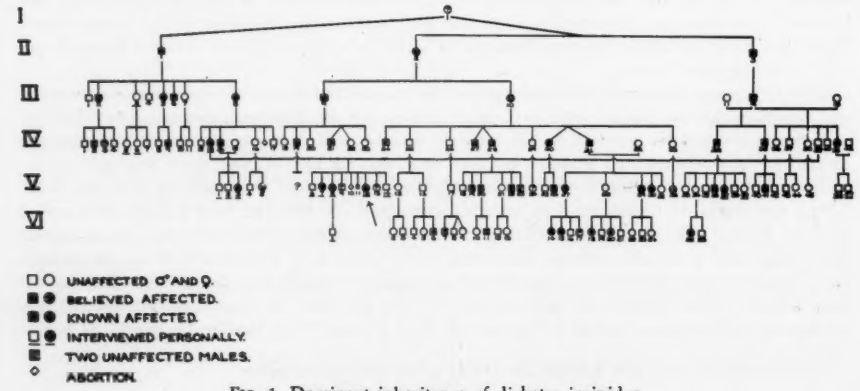

Fig. 1. Dominant inheritance of diabetes insipidus.

of Waterman, suggesting that diabetes insipidus may, even at that time, have been recognized as a family characteristic. She had at least three children, concerning whom no medical data are available other than that they were "drinkers."

Generation III: There were seven individuals in this generation, none of whom were seen by the authors. They are: III-2 III-5 and III-9 who died in old age of unknown causes; III-6, aged 67, who refused to cooperate in the investigation, because of some unspecified illness; III-8, the grandmother of the proband, who was obese, and died at the age of 39 years, of what was said to be gallbladder disease; III-10, who was also obese, and died at age 77 years of "the dropsy"; III-12, who died at age 72 years, also of "the dropsy."

Generation IV: In this generation there were 14 affected individuals, five of whom were seen by the authors. IV-2 was killed in an accident at about 50 years of age, but was stated to have been in good health, apart from his polydipsia and polyuria, until his death. IV-9, aged 45, is affected but otherwise in good health.

IV-13, the mother of the proband, has suffered from polydipsia and polyuria since infancy, drinking an average of 4½ quarts of water a day, and having to get up at least twice every night. She thinks that the condition has been slowly decreasing in severity since the birth of the proband (when she was 32 years old), but that she drinks and urinates more than usual when she has a fever, or exercises strenuously (although no effect of fever on urinary output could be demonstrated during several febrile episodes while in hospital). A marked increase in water intake and output is stated to occur during pregnancy. When fluid is restricted her mouth and throat feel very dry, and she complains of a gnawing, crampy epigastric pain.

From the age of 15 years on she has suffered from intermittent attacks of pyelonephritis, and on several occasions she was admitted to the Royal Victoria Hospital of Montreal, where her records have provided much useful information. During these admissions her urinary specific gravity ranged from 1.002 to 1.009. On two occasions, however, it rose to 1.020 or more, and it is interesting to note that on both these occasions the patient was in labor (at the birth of V-12 and V-13, respectively), but that no pituitrin had been given. Examination of the genitourinary tract when the patient was 32 years old revealed a mild hydronephrosis and a marked hydroureter on the right side and an incomplete double renal pelvis on the left side. The bladder capacity (gravity fill) was 2000 cc. The rate of phenolsulphonephthalein excretion was normal on several occasions.

At the age of 42 years, when first seen by the authors, she was in good health, and not pregnant. Her urinary specific gravity was 1.001. After she was given pitressin tannate in oil 2 pressor u. intramuscularly, she passed no urine for six hours (a remarkable feat, for her), and the specific gravity rose to 1.007. The following morning, 14½ hours after the injection, the specific gravity of the urine was 1.014. The following year she was seen again, in the sixth month of her tenth pregnancy, and reported a marked increase in her polydipsia and polyuria, as with all her previous pregnancies. The urinary specific gravity was again 1.001.

IV-14 was seen when he was 38 years old. He dates the onset of polydipsia and polyuria to early infancy. He drinks 15 to 20 quarts of water a day and is obliged to get up 6 to 8 times every night. There is no obvious increase in intake with fever, or with exercise. When fluid is restricted he has a sensation "like fire in the stomach" and sometimes feels "kind of faint." The specific gravity of his urine was 1.002. An intramuscular injection of aqueous pitressin 3 u. was followed by a rise in the urinary specific gravity

to 1.006 within 30 minutes, after which time no further observations could be made.

IV-27 is one of a pair of twins who are said to resemble each other closely. He has confirmed by letter the impression that he is affected, and drinks about 10 quarts of water a day. His co-twin, IV-28, is also believed to be affected.

IV-30, one of a pair of dizygotic twins, has written that she has the condition and drinks "several quarts" of water a day.

IV-31, the co-twin of IV-30, was seen at the age of 56 years. He drinks 4 gallons or more of water a day and has to get up once or twice every night. He has "always had it." He needs to drink more than usual when he has a fever, but not when he exercises strenuously. When his fluid intake is restricted his tongue feels very dry and he "would go wild if he couldn't get water" but there is no abdominal pain. The specific gravity of the urine was 1.001. Because of his elevated blood pressure (160/104 mm.Hg) no pitressin was given.

IV-34 was seen when he was 65 years old. He stated that he had always had the disease, but that it had "slowed down" at the age of 28 years. He still drinks 3 to 4 quarts a day and gets up twice a night to urinate.

IV-41 was seen when she was 43 years old. She has had polydipsia and polyuria since childhood, drinks five quarts or more of water a day and gets up twice a night. Her fluid requirements are increased when she has a fever, and when she exercises strenuously. Fluid restriction makes her "terribly thirsty" but does not cause abdominal pains. Her urinary specific gravity was 1.002 but in view of a somewhat elevated blood pressure (156/96) no pitressin was given.

IV-19, 21, 24 and 35 are believed to be affected, but were not interviewed.

IV-5, 6 and 39 were seen and found not to be affected.

Generations V and VI: V-3 is the subject of Case 2.

V-7 and 8, aged 22 and 21 years, respectively, were seen briefly by the authors while they were visiting Montreal. They both drink 7 to 10 quarts of water a day, and their urinary specific gravities were 1.001 and 1.002, respectively. V-8 was given an injection of pitressin in oil and reported a marked reduction in urinary output, which lasted 48 hours.

V-9 died at the age of 1½ years of "membranous croup," and V-13 died 20 hours postpartum of prematurity and intracranial damage.

V-19, 20 and 22 are believed to be affected but were not seen.

V-27 states in a letter that she has had the condition since 3 to 4 years of age and drinks a great many glasses of water a day. Her first two children, aged 11 and 8 years, respectively (VI-14, 15), have the condition, the third and fourth, aged 3 years and 1 month, respectively (VI-16, 17), show no signs of the disorder so far.

V-29, aged 22 years, states in a letter that she drinks a gallon or more of water a day. The condition was first noticed at 3 or 4 years of age. Her three children, aged 3, 2 and 1 years, respectively (VI-22, 23, 24) show no signs of the condition as yet.

V-30 was seen when she was 17 years old. Her excessive fluid requirements were first noted when she was 5 years of age. She estimates that she now drinks about three gallons of water a day, and more when she has a fever or exercises strenuously. When her fluid intake is restricted her mouth gets dry but she does not have any abdominal pains. Her urinary specific gravity was 1.001.

V-36 was mentally deficient and died in an institution at age 18 years of bronchopneumonia. His father stated that this boy was affected.

V-30 was admitted to the Royal Victoria Hospital in 1932 with a diagnosis of rickets, scurvy and mental retardation. Chronic thirst and urinary frequency were noted. Mosenthal-concentration tests caused an elevation of the urinary specific gravity to 1.015 on one occasion and 1.017 on another. She was given pituitary extract 0.25 cc. daily for several days with no effect on the water output, and it was therefore concluded that she "did not have a typical diabetes insipidus." The authors were unable to see this girl. Her father states that she is a "drinker."

V-1, 2, 6, 14, 31, 39, 46, 47 and VI-1, who are all over 2 years of age, were seen and found not to be affected.

Discussion

Symptomatology: The existence of families in which a rare hereditary disease occurs with a high frequency provides a unique opportunity to study the life-history of the disease, for within such a family the etiologic agent (the defective gene) is constant, and what is virtually the same disease may be observed simultaneously at various stages in its course.

Nevertheless when one reviews the symptomatology of diabetes insipidus within the family described above, one is struck by the rather high degree of variability between family members. The average daily fluid intake reported by adult family members varied from 3 to 4 quarts a day (IV-34) to 15 to 20 quarts a day (IV-14). There was also a good deal of day-to-day variation for individual members, and in some cases the daily output was so small (less than a quart on one occasion in Case 1) that some doubt was for a time cast on the diagnosis. However, the lack of response to intravenous saline and the definite response to pitressin in Cases 1 and 2 leave little room for doubt that the disease is diabetes insipidus. It should therefore be emphasized that an exceedingly great urinary output is not a requisite for making this diagnosis.

Four of the six affected individuals questioned reported an increase in fluid intake and output with fever, yet the patients described in Cases 1 and 2 while under observation in hospital did not show any changes in water balance or urinary specific gravity associated with fever. This observation agrees with that of Forssman[5] who found in five adult hospital patients with hereditary diabetes insipidus that fever caused no significant alteration in urinary output.

Three of six patients questioned reported an increase in fluid requirements with exercise, and one reported a seasonal variation (IV-14), but no objective tests were done to verify these impressions. Two of four individuals interviewed who were over the age of 40 years reported decreasing fluid requirements after the third decade. This impression has been reported many times in the literature, and has received objective confirmation from the observations of Forssman.[5] IV-13 reported a definite increase in her fluid intake and output during each of her 10 pregnancies, regardless of whether the baby subsequently developed diabetes insipidus. A similar phenomenon has been reported by Ellerman.[9]

The disease does not seem to have any deleterious effect on the general health of the affected individuals who regard it, more or less philosophically, as a nuisance, since they cannot maintain any occupation for more than an hour or so without interrupting it to have a drink and urinate. This sort of nuisance may be a serious economic handicap to a man who works at an occupation such as haying, where his working efficiency is impaired by the necessity of frequent visits to a source of water. It may also be serious when affected individuals are admitted to hospital for medical or surgical treatments

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where limitation of fluid intake is imposed, without recognition of the diabetes insipidus. Awareness of the condition at such times, and administration of pitressin may be of great benefit to the patient's comfort and well-being.

Many affected individuals survive well into old age, and there seems to be no gross diminution of the life span due to the disease but, as has been pointed out by Forssman,[5] one could detect only very obvious deleterious effects from data such as presented here. One does not know, for example, how many afflicted individuals in this family died in early childhood from dehydration exacerbated by an unrecognized diabetes insipidus. It is difficult to decide whether IV-13's genitourinary troubles are due to her diabetes insipidus, but in view of the report by Weller[10] of similar urinary tract changes associated with diabetes insipidus, this possibility must be kept in mind. It is interesting to note that the kidney of an affected individual is, under some conditions, able to concentrate urine quite well. The specific gravity of IV-13's urine during labor was on two occasions recorded as 1.020 or more. This suggests either that the posterior pituitary or some other gland may in such persons sometimes put out a hormone with antidiuretic effect, or that the kidney can sometimes concentrate urine adequately in the absence of antidiuretic hormone (perhaps due to deficiency of the diuretic hormone of the anterior pituitary). A third possibility, suggested by Stehle,[11] is that pitocin, when excreted in large quantities as in labor, may be transformed into pitressin.

Genetics: It is evident that the pattern of inheritance of the disease fits the expectation for a simple Mendelian dominant factor:

1. As far back as the information is reliable, every affected person has an affected parent.

2. The proportion of affected to nonaffected persons in the offspring of affected individuals does not differ significantly from 1:1. Considering only generations III to IV inclusive, where the information is reasonably reliable, there are 86 classifiable offspring of affected individuals of which 37 (44%) are affected (counting IV-27 and 28, who are probably identical twins, as one individual). This does not differ significantly from the theoretic expectation of 43 ($\chi^2 = 1.774$, $P = 0.2 - 0.1$).

3. With dominant inheritance one expects equal proportions of affected males and females. In this family there are 21 males and 16 females affected which is again not significantly different from the theoretic value of 18.5:18.5 ($\chi^2 = 0.6756$, $P = 0.5 - 0.3$).

The fact that the proband's parents are second cousins is of no significance with regard to the diabetes insipidus.

Sex-linked dominant inheritance is ruled out by the fact that several males have transmitted the disease to their sons, and the data do not provide any basis for suspecting partial sex-linkage. (This point will be discussed more fully in a subsequent publication.) It is therefore justifiable to conclude that the gene responsible for the appearance of diabetes insipidus in this family is inherited as a simple Mendelian dominant. The authors were unable to trace any connection between the present family and a Canadian family reported by Chase[12] which also showed dominant inheritance.

Most of the reported cases of hereditary diabetes insipidus have shown simple dominant inheritance, perhaps to some degree because this is the easiest type of inheritance to detect. The most outstanding example is the family reported by the Weils[13] which at the time of the last report[14] included 37 affected individuals in six generations, nearly all of whom were directly investigated. However, it has been shown by Forssman[5] that in some families the disease shows sex-linked recessive inheritance, which may account

for the reported excess of affected males. In another family, described by Forssman,[5] also showing sex-linked recessive inheritance, the affected males did not respond to pitressin, suggesting that this family may have had the "nephrogenic" type of polydipsia and polyuria, rather than the pitressin-deficiency type.

It is difficult to estimate what proportion of all cases of diabetes insipidus are due to a defective gene, although the proportion is thought to be fairly small. Levit and Pessikova[15] found that in a series of 13 cases of "idiopathic" diabetes insipidus only three were familial, but their diagnoses were not confirmed by testing the response to pitressin. Jones[16] studied 42 cases of diabetes insipidus seen in one hospital over a 17 year period and did not classify any of them as hereditary. However, his diagnostic criteria were so severe that many of the individuals reported in the present paper would not have fallen into his group. It must also be stressed that in order to establish a case as being hereditary, the first requirement is that the patient shall be asked whether there are other cases of polydipsia and polyuria in the family, and that this is not always done. Several members of the family reported in this paper have been in various hospitals, sometimes with nocturia, frequency, etc., listed among their complaints, but without recognition of their rather outstanding family history. This greatly increases the difficulty of estimating the incidence of hereditary diabetes insipidus.

It is suggested that this family demonstrated how a routine inquiry about similar conditions in the patient's relatives[17] can be of definite diagnostic value. Awareness of the condition can be helpful insofar as it reduces the amount of necessary investigative procedure, and in that pitressin can be given to save the patient discomfort on occasions where it is desirable to limit fluid intake.

Summary

The clinical features of diabetes insipidus are described in a family showing dominant inheritance of this condition. Forty affected individuals in six generations are listed. Two members of the family, investigated in hospital, showed no alteration of urinary flow in response to the intravenous injection of saline, but a marked reduction in flow following the injection of pitressin, thus confirming the diagnosis of diabetes insipidus due to pitressin deficiency. An exceedingly great urinary output is not necessarily a feature of the disease. The diagnostic value of the family history is emphasized.

Acknowledgments

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SPANISH ABSTRACT

Herencia Dominante en la Diabetes Insípida Estudio en una Familia

Los autores presentan el estudio de una familia de "bebedores" en la que los miembros afectados sufrían de diabetes insípida, padecimiento que aparecía tan frecuentemente en la familia que la reconocieron como una característica familiar.

En total, cuarenta individuos heredaron la enfermedad a través de seis generaciones. En dos miembros de la familia que se estudiaron en el hospital no hubo alteración del débito urinario como respuesta a la inyección intravenosa de solución de cloruro de sodio pero sí presentaron reducción marcada del débito urinario después de la inyección de pitresin confirmándose así el diagnóstico de diabetes insípida debida a deficiencia de pitresin. Se hace hincapié en que no necesariamente la eliminación excesiva de orina sea una característica de la enfermedad y en el valor diagnóstico de los antecedentes del padecimiento en otros miembros de la familia.

1615 Cedar Avenue

CLINICAL DIAGNOSIS OF ENDOCARDIAL FIBROSIS

Analysis of Literature with Report of Four New Cases

By EDWARD C. LAMBERT, M.D., CLARE N. SHUMWAY, M.D., AND KORNEL TERPLAN, M.D.
Buffalo, N.Y.

ENDOCARDIAL fibrosis (also termed endocardial sclerosis and endocardial fibroelastosis) is now recognized as a pathologic entity occurring in infants and carrying a grave, if not universally fatal, prognosis. In the past 10 years publications have dealt chiefly with the morphologic findings and possible etiology of the disease and with the mechanism of cardiac failure. They have separated it as a pathologic entity from the conglomerate group of diseases termed idiopathic cardiac hypertrophy. Recent reports have emphasized the clinical features manifested by infants with the disease. Cases have not been reported in which the condition was correctly diagnosed during lifetime, and clinical diagnostic criteria have not been laid down.

The purpose of this communication is to discuss the diagnostic possibilities and to present four cases seen by the authors in the past two years. In two* of these cases the clinical diagnosis was correctly made before death. The additional finding in each of the four cases which aided in the diagnosis is that of evidence of left ventricular hypertrophy in the precordial leads of the electrocardiographic tracing.

CASE REPORTS

Case 1. L.M., white female infant, was seen for first time at 7 wk. of age because of grunting respirations of 2 wk.' duration and progressively increasing dyspnea of 2 days' duration.

During 1st 7 wk. of life infant had remained free of infections but had gained only 210 gm. above birth weight.

Admission examination revealed a scrawny, seriously ill infant with rapid (50 to 60/min.) tugging respirations, pulse rate 150/min., and a normal temperature. Left cardiac border extended to 6th ICS. in anterior axillary line. Gallop rhythm was present but no murmurs were heard. Lungs were clear. Liver extended 3 cm. below R costal margin. There was no cyanosis nor was there any edema of the extremities. Femoral pulsations were felt on both sides.

Chest RG disclosed heart to be markedly enlarged. Blood count and urinalyses were normal. First ECG included only 3 standard limb leads. This was nondiagnostic.

Clinical impression was that of congestive heart failure, due either to myocarditis or a congenital cardiac anomaly. Infant was treated with oxygen, morphine and digitalis and improved within a few days.

From time of first admission until death at age of 3 yr., child had 9 admissions to hospital and spent much of her life in a convalescent home associated with the hospital. Despite improvement on digitalis, she remained dyspneic on exertion and developed poorly, weighing only 9.9 kg. at age of 3 yr. She was very susceptible to respiratory infections and each hospital admission was precipitated

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* Since submission of this manuscript, another clinically diagnosed case has been seen by the authors. Diagnosis was made on the basis of the criteria outlined below, including the characteristic findings in the precordial ECG, and confirmed by autopsy.

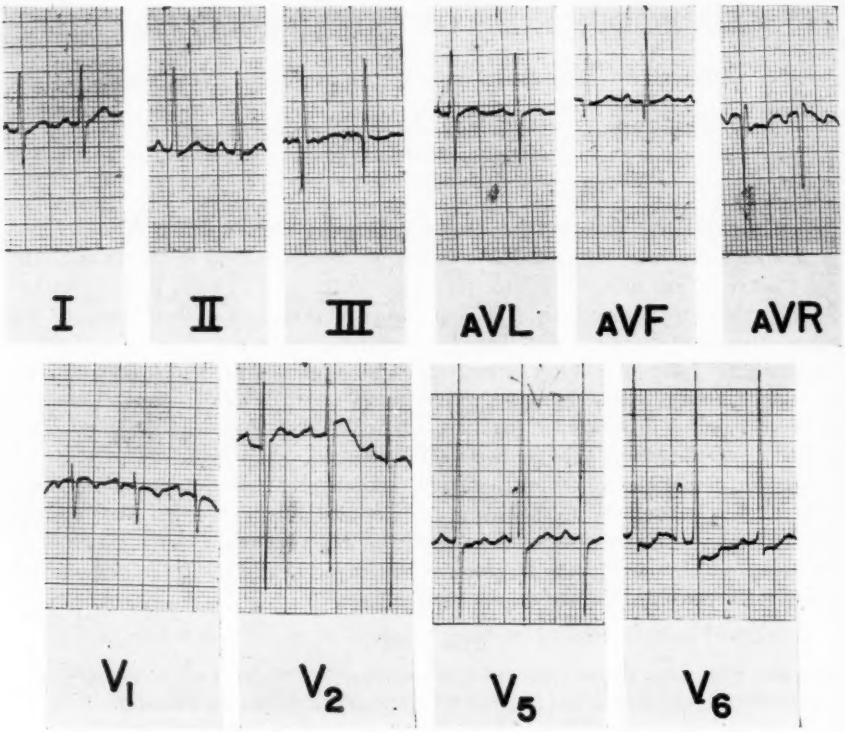

FIG. 1. (Case 1, L.M., 8 mo.) ECG showing tall delayed R-wave in lead V_6.

by a pharyngitis or pneumonia. At no time, except just before death, did she manifest cyanosis. No murmur was heard on many examinations.

At age of 8 mo., she had 1st ECG (Fig. 1), which included all precordial leads and disclosed evidence of L ventricular hypertrophy manifested by a tall delayed R-wave in lead V_6. Because of this finding, the diagnosis of endocardial fibrosis was entertained at this time.

Three years after first admission she developed what appeared to be R lower lobe pneumonia, which seemed to precipitate congestive cardiac failure. Despite all the usual efforts, she died within 2 days. Electrocardiogram taken a few hours before death revealed the first significant change in electrocardiographic tracings which had occurred in 2 yr. period. This final tracing showed evidence of changing myocardial disease and probably R ventricular hypertrophy. Previously present evidence of L ventricular hypertrophy had disappeared.

Autopsy (Dr. Dorothy Shaver): Heart was markedly enlarged, weighing 110 gm. It extended far over into L thoracic cavity compressing L lung. Pericardial sac contained approximately 30 cc. of straw-colored fluid. Entire heart appeared markedly dilated, especially L ventricle. Wall of L ventricle measured 8 mm. in thickness while that of R ventricle appeared hypertrophic and measured 7 mm.* There was marked endocardial and subendocardial fibrosis in L ventricle and auricle, but only slight involvement of R ventricle by the same process. Mitral valve showed some fibrosis of posterior leaflet which was small and adherent to posterior wall. Other valves were normal. No other structural anomalies were present.

Lungs showed pulmonary edema and pneumonic changes.

* It was believed that previously present L ventricular hypertrophy, for which there was electrocardiographic evidence, had given way to dilatation and thinning of ventricular wall and that a R ventricular hypertrophy had developed later.

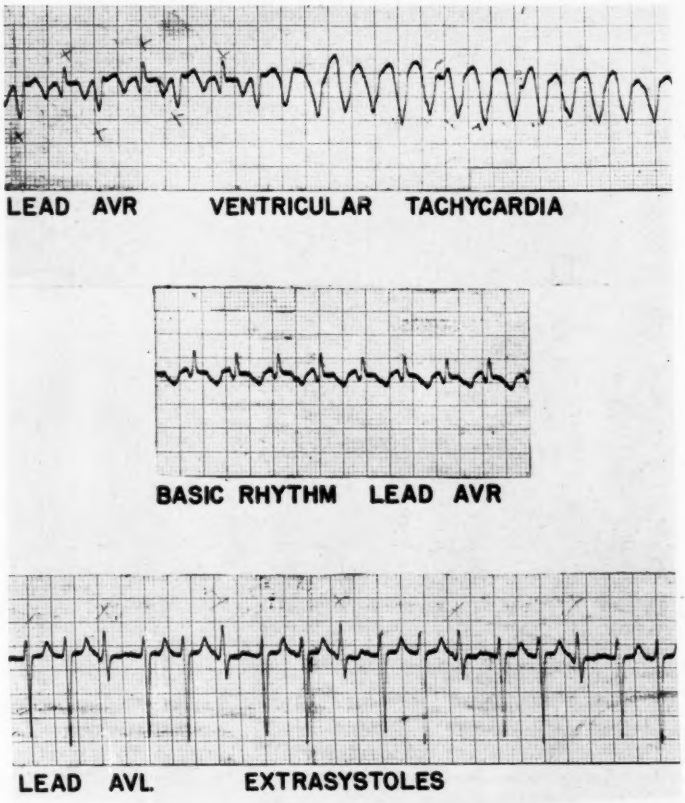

FIG. 2. (Case 2, J.L., 4 mo.) Endocardial fibrosis. ECG showing initial arrhythmia.

Microscopic examination of cardiac muscle showed typical changes of endocardial fibrosis. These changes were most marked in L auricle and L ventricle but were also present to a slight extent in R ventricle. There were no active inflammatory changes in the myocardium.

Histologic examination of lung confirmed gross diagnosis of extensive edema with some areas of pneumonitis.

Case 2. J.L., 4 mo. old white male infant, was admitted to hospital with history of irritability and progressively increasing dyspnea and pallor of 4 days' duration. Prior to onset of present illness, he had been entirely well.

Admission examination disclosed a well-developed infant who appeared seriously ill with marked dyspnea, pallor and perioral cyanosis. Respiratory rate was 90/min., cardiac rate 180/min., temperature 38.8°C. Lungs were clear to percussion and auscultation. There was no evidence of an upper respiratory infection. Heart was irregular with poor tones and a gallop rhythm. There was no definite murmur audible. Liver edge was palpated 4 to 5 cm. below R coastal margin. There was no edema of extremities. Femoral pulses were palpable.

Blood count and urinalysis were normal. Chest RG revealed enlargement of heart with no evidence of pneumonia. Shortly after admission an ECG showed numerous extrasystoles arising from varying ventricular foci, and occasional runs of ventricular tachycardia (Fig. 2).

Intravenous administration of quinidine lactate* was followed almost immediately by temporary

* Quinidine lactate for intravenous use was kindly supplied by Eli Lilly and Company.

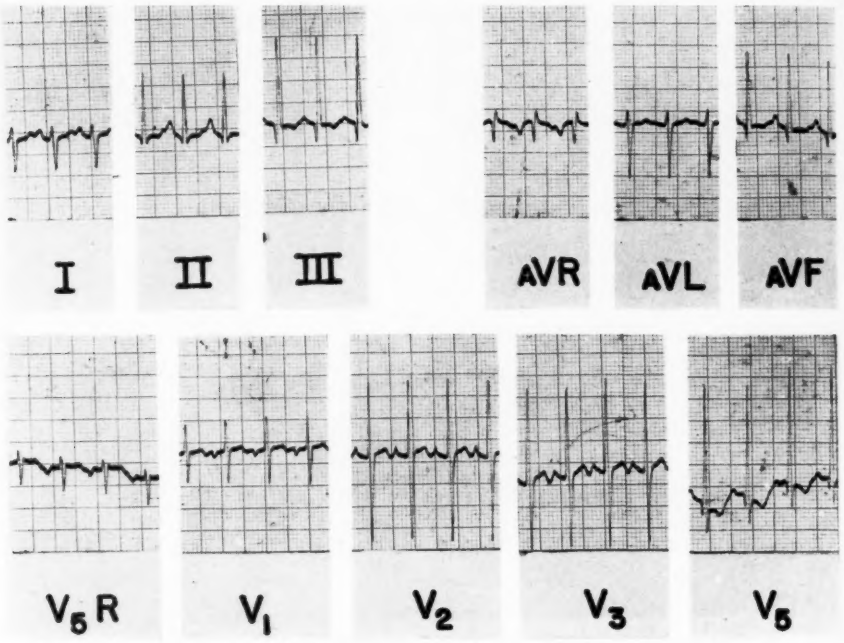

FIG. 3. (Case 2, J.L., 4 mo.) ECG showing tall delayed R-waves with inversion of T in V_5.

disappearance of these abnormalities and a slight clinical improvement. Because of persistence of tachycardia, dyspnea and enlargement of liver, patient was digitalized. On several occasions extrasystoles and runs of paroxysmal ventricular tachycardia were recorded. These could be abolished temporarily by use of quinidine. During one of the periods of their absence, ECG revealed evidence of L ventricular hypertrophy in precordial leads (Fig. 3).

Approximately 24 hr. after admission patient suddenly became apneic, developed marked bradycardia and shortly thereafter died.

Autopsy (Dr. Kornel Terplan): Heart was markedly enlarged and somewhat globular in shape. Shining through thin epicardium, there were some areas, especially in posterior wall of L ventricle and anterior wall of R ventricle, with a peculiar grayish-yellow sheen. Bulk of myocardium appeared red in color. Endocardium of dissected heart appeared slightly fibrous, especially in anterior portion of interventricular septum. Valves were all intact.

Wall of L ventricle measured 13 mm. in thickness, that of R 4 to 5 mm. Weight of heart was 75 gm. Other abnormalities were not encountered.

Histologically L ventricular myocardium showed typical endocardial fibrosis which extended only slightly into inner muscle layer. Left auricle showed same changes while in comparison, R ventricular endocardium was involved to only a slight degree.

Case 3.* R.L.J., white female infant, was admitted at 2½ mo. of age because of rapid respirations of 24 hr.' duration.

She had been examined frequently by referring physician. No evidence of heart disease had been found. She had gained well and had developed normally until 3 days prior to admission. At that time she became irritable and had an occasional choking spell while eating. Suddenly 24 hr. before admission, she became pale and dyspneic.

Physical examination disclosed a pallid but well nourished severely ill infant. Respirations were labored and rapid at a rate of 90/min. Pulse rate was approximately 190/min. She was afebrile. No

* This case report is presented through courtesy of Dr. Robert Warner, referring physician.

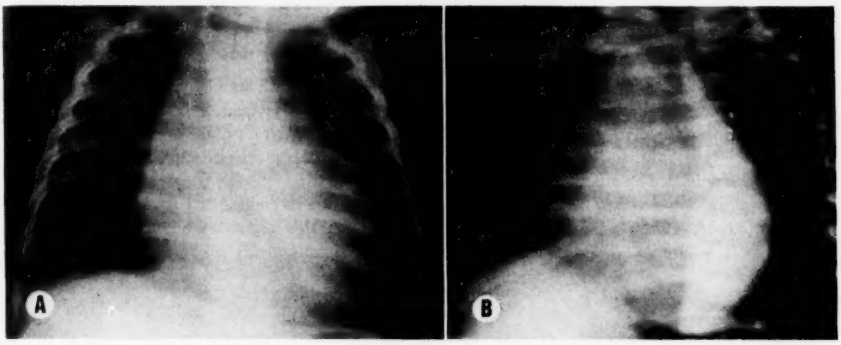

FIG. 4. (Case 3) (A) Anterior and (B) left anterior oblique RGs of chest showing marked cardiac involvement.

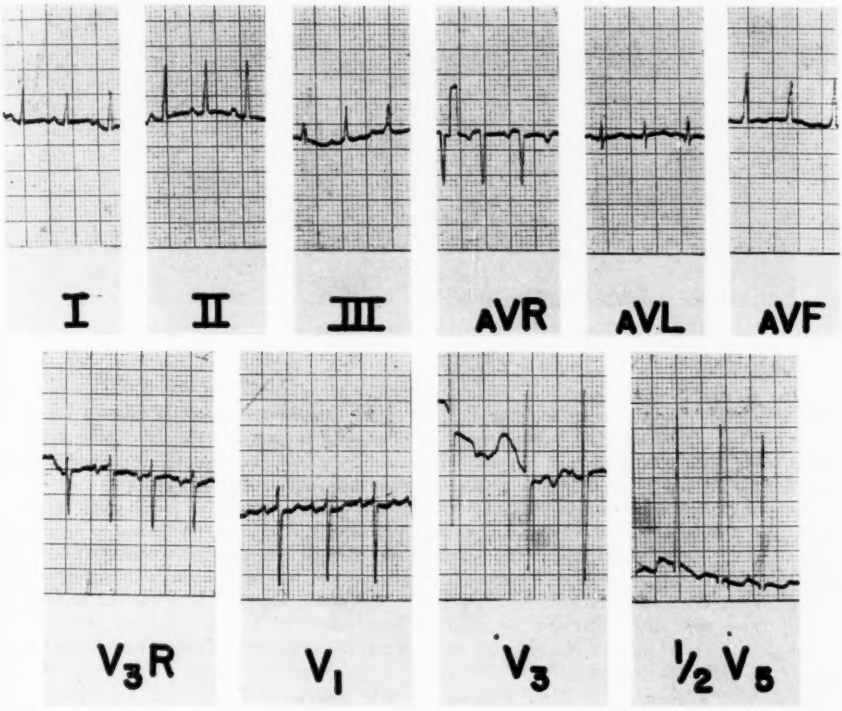

FIG. 5. (Case 3, R.L.J., 2½ mo.) ECG showing tall delayed R-wave and inverted T-wave in V_3 (half standardization).

sign of infection in upper respiratory tract was apparent. Lungs were clear. Heart was enlarged and tones were poor and there was a gallop rhythm. No murmur was audible. Liver was palpable 3 cm. below R costal margin. Femoral pulsations were easily palpated.

Urinalysis and complete blood count were normal. Chest RG disclosed a large cardiac shadow with no evidence of pneumonia (Fig. 4). Fluoroscopy, several days later, revealed cardiac enlargement to be diffuse, involving all 4 chambers. Electrocardiogram taken on night of admission (Fig. 5) showed rate of 193/min. and normal axis position. Precordial leads revealed evidence of L ventricular hypertrophy manifested by a tall delayed R-wave in lead V_5.

Initial impression was that patient was in cardiac failure due to endocardial fibrosis. Therapy consisted of oxygen, morphine and digitalis. She improved on this regimen and was discharged on digitalis therapy after 12 days in hospital. She remained asymptomatic at home for 1 mo., when

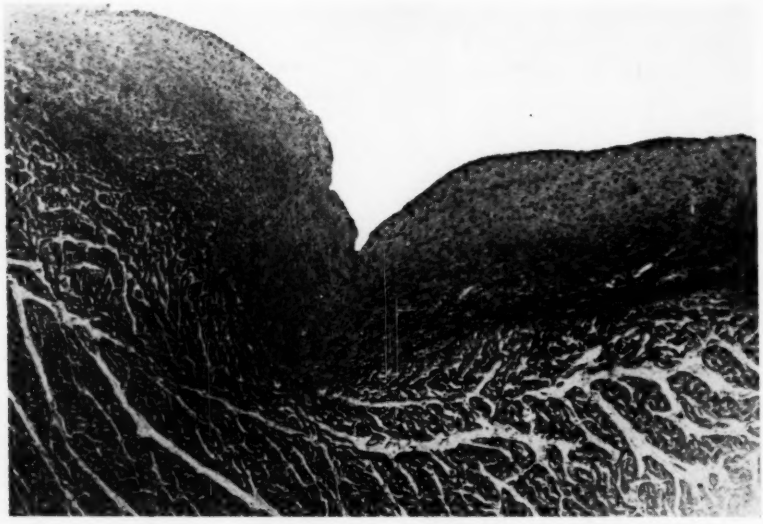

FIG. 6. (Case 3). Cross section of portion of L ventricle. Characteristic appearance of endocardial fibrosis.

irritability and dyspnea recurred and she was readmitted to hospital. Again she showed evidence of cardiac failure. Repeat ECG was similar to previous tracings showing evidence of L ventricular hypertrophy. With same therapy of oxygen, morphine and digitalis, she improved for a period of 5 days. On 6th day she suddenly became cyanotic with gasping respirations and died.

Autopsy (Dr. Kornel Terplan): There was unusually marked congestion of all veins of neck. Heart was globular in shape and markedly enlarged. Most of this enlargement seemed to be due to increase in size of L ventricle. Wall of L ventricle was 8 to 10 mm. thick; R ventricle was 2 to 3 mm. thick. Inner surface of L ventricle and L auricle showed typical appearance of diffuse endocardial and subendocardial fibrosis. Endocardium of R ventricle and R auricle did not show this change. There were no valvular or other structural abnormalities of heart or great vessels.

Lungs were not edematous. No aspirated material was found in tracheobronchial tree. Liver was markedly enlarged and congested.

Microscopic examination of heart revealed moderate endocardial fibrosis and some edema of thickened endocardium. There was distinct and somewhat more diffuse reticulated scar formation throughout myocardium. Epicardium was thickened and showed some round cell infiltration. Fibrotic and edematous areas in myocardium, representing reticular pattern of scarring, were seen around and between atrophic muscle fibers (Fig. 6).

Case 4. I.D., American Indian female 4 mo. of age, was admitted to the hospital because of

anorexia and a weak cry of 5 days' duration. On day of admission she developed rapid, noisy respirations.

Prior to onset of present illness, infant had been well and had doubled birth weight.

Physical examination on admission revealed a well-nourished infant in moderate respiratory distress with a respiratory rate of 60/min. There was slight suprasternal tugging. Cardiac tones were poor, rate was rapid. No murmur was heard. Liver was enlarged and palpable 2 to 3 cm. below R costal margin. There was evidence of a mild upper respiratory infection. Lungs were clear. No cyanosis or clubbing of extremities was present. Femoral pulsations were easily palpable.

Urinalysis and blood count were normal. Chest RG revealed marked enlargement of heart with no evidence of pneumonia. Several days after admission chest fluoroscopy revealed enlargement of

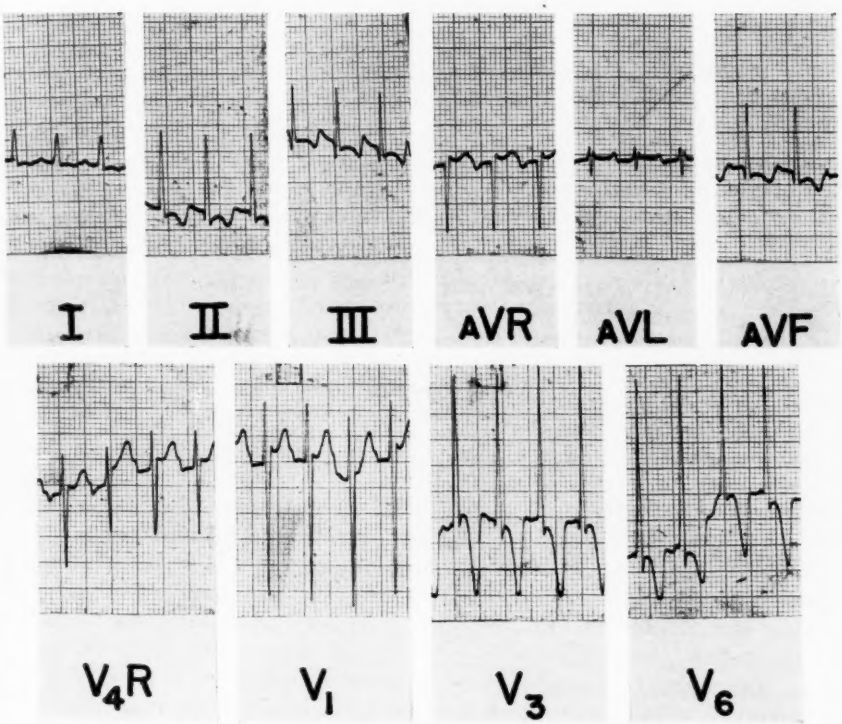

FIG. 7. (Case 4, I.D., 5 mo.) ECG showing tall delayed R-wave and extreme inversion of T-wave in V_5.

all 4 chambers and evidence of pulmonary congestion. Electrocardiogram taken shortly after admission revealed a supraventricular tachycardia at a rate of 180/mm. and evidence of L ventricular hypertrophy in precordial leads (Fig. 7) manifested by tall delayed R-waves in lead V_6 with deep inversion of T-wave. Second ECG 1 wk. after admission revealed no significant change except for development of a first degree A-V block.

On admission to hospital, it was believed that patient was in cardiac failure, possibly due to a myocarditis. Following treatment with oxygen, morphine, digitalis and penicillin, she gradually improved. Within 1 wk. she was able to remain out of oxygen tent without dyspnea. At that time a faint blowing systolic murmur was audible at L sternal border. Cardiac tones were again noted to be distant, having a poor quality.

Rather suddenly on 12th hospital day she developed fever, became increasingly dyspneic, and for first time, cyanotic. Shortly thereafter she died in a shock-like state.

Autopsy (Dr. Kornel Terplan): Heart was markedly enlarged, weighing 83 gm. Left ventricle was considerably hypertrophic and dilated. Its wall was 10 mm. thick while that of R ventricle varied between 2 and 5 mm. in thickness. Undissected heart showed a diffusely grayish-yellow color, more marked in L ventricle. There was prominent fibrosis of endocardium with thick whitish strands surrounding myocardial fibers of inner myocardium. These changes were present to greatest extent in wall of L ventricle and auricle. No valvular or other structural abnormalities were noted.

Microscopic examination of heart disclosed moderate fibrosis of endocardium with subendocardial extensions between muscle fibers. There was distinct edema within this fibrous tissue between these muscle fibers and in outer myocardium.

The only other pathologic finding of note was moderately severe rickets at costal cartilaginous junctions.

Discussion

The Clinical Picture: In an attempt to obtain a clearer picture of the usual clinical findings in this disease, the authors analyzed a total of 94 cases (15 from autopsy files of this hospital, the rest gathered from the available literature[1-22]). Inasmuch as endocardial fibrosis is a frequent finding in association with both coarctation of the aorta and anomalies of the coronary artery and is considered to be secondary to these abnormalities,[23,24] no case among the 94 reviewed was included with either of these findings, nor

TABLE 1

Findings in Cases of Endocardial Fibrosis

(Data Gathered from 89 Reported Cases and 15 Cases from Buffalo Children's Hospital)

	Cases with Significant Valvular Involvement		Cases without Significant Valvular Involvement		Total	
	%	No.	%	No.	%	No.
Death at Age of 1 Yr. or Less	97%	31* — 32†	86%	53 — 62	92%	84 — 94
Dyspnea	81%	22 — 27	96%	50 — 52	91%	72 — 79
Cyanosis either absent, intermittent or terminal	55%	22 — 40	90%	34 — 38	72%	56 — 78
Murmur absent or faint	50%	13 — 26	9[illegible]%	38 — 44	79%	51 — 70
Cardiac enlargement on chest RG	82%	14 — 17	100%	34 — 34	94%	48 — 51
Left ventricular hypertrophy isolated or of much greater degree than right ventricular hypertrophy	58%	18 — 31	80%	47 — 59	72%	65 — 90

* Numerator = number of cases with pertinent finding.

† Denominator = Total number of cases where information was available.

were any cases included with other significant gross anomalies of the heart. Because of the possibility of severe valvular stenosis or atresia producing mural endocardial fibrosis, the cases were subdivided into those with and without serious valvular lesions.* This analysis yielded the following information (table 1).

Age and Sex: The age at death ranged from birth to 8 years with the highest frequency between 3 and 6 months. Ninety-two per cent of the deaths occurred during the first year of life. There was a slight preponderance of males.

Symptoms and Signs: Dyspnea, frequently accompanied by a cough, was the most common and most marked manifestation occurring in 91% of the 79 cases where such data were recorded.

Cyanosis, while a common finding, was absent, intermittent or only terminal in 72% of the 78 cases in which this sign was recorded. Except for the patients who died during the first few weeks of life, there was only one case in which definite persistent cyanosis was reported.

Murmur: There was no heart murmur or only a faint one in 79% of 70 cases where such data were recorded. When the authors considered the 62 cases where, at autopsy, the valvular involvement was insignificant, this figure rose to 95%. Thus the finding of a loud murmur would seem to depend on an underlying valvular involvement.

Other symptoms which were frequently noted were fever (12), irritability (10), retarded growth or weight loss (9), anorexia and feeding difficulties (12) and vomiting (10). Many of these patients thrived for several months, then died shortly after the first onset of their symptoms. Three of them died suddenly without preceding symptoms.

Cardiac enlargement on roentgenographic examination, like dyspnea, was almost invariably present. It was found in 94% of the 51 cases where films were taken. In the four cases reported in detail here, the enlargement was marked and involved all four chambers.

Electrocardiographic changes in the 23 cases where tracings were made, not including the four cases described in this report, revealed no specific pattern. Pathologic T-wave changes were found in 7 patients, right axis deviation in 6,† A-V block in 5, and complete left bundle branch block in 2. Two cases were reported with complete heart block. In the cases reported in the literature, no description of precordial leads was recorded.

Left Ventricular Hypertrophy: Most authors have noted the marked tendency for the left ventricle to be involved in the pathologic process. There has usually been an associated hypertrophy of that chamber. This analysis revealed that 72% of the 90 cases where adequate data were recorded showed either isolated left ventricular hypertrophy or hypertrophy of the left ventricle of a much greater degree than that found in the right ventricle (table 1). (It is of interest that in the 59 cases where there was no marked valvular involvement, the figure was 80%.) Thus it seems reasonable to presume that, if multiple precordial leads had been taken, a majority of the cases would have shown electrocardiographic findings similar to those in the four cases reported here.

The electrocardiographic features of left ventricular hypertrophy have been clearly outlined by Wilson and his co-workers.[25] Sokolow and Lyon[26] have defined the criteria by which the diagnosis of left ventricular hypertrophy can be made electrocardiographically with a high degree of accuracy. However, their standards do not pertain to infants. Comparing the electrocardiographic findings in the present four cases with the limits of

* The 15 cases gathered from files of this hospital did not have valvular involvement.

† The electric axis in the other cases was not mentioned.

TABLE 2

ELECTROCARDIOGRAPHIC EVIDENCE OF LEFT VENTRICULAR HYPERTROPHY IN FOUR CASES OF ENDOCARDIAL FIBROSIS

Feature Indicating Left Ventricular Hypertrophy	Limits of Normal Variability[27]	Findings in Reported Cases			
		L.M.*	R.J.	J.L.	I.D.
1. Tall R in V_5 and V_6	R-wave 26 or less in 97 of 98 normal infants between 1 day and 12 mo. of age (measured in 0.1 mv.)	34	60	26	35
2. Delay of RS in V_5 and V_6	† Time of onset of RS deflection .035 sec. or less in 93 of 94 infants between 1 day and 12 mo. of age	.04	.05	.05	.04
3. Prominent Q in V_5 or V_6		0	0	+	+
4. Deep S in V_3R and V_1		0	+	0	+
5. Inversion of T in V_5 and V_6	Not found in 101 cases of normal infants between 6 mo. and 12 mo. of age	+	+	+	+

* Tracing taken at 8 mo.

† Tracings presented not taken simultaneously with lead I as done by Ziegler. Measurements taken from beginning of QRS in V_5 and V_6, respectively, with aid of magnifying glass.

variability for normal infants published by Ziegler,[27] it seems clear that evidence of left ventricular hypertrophy was present in each of the four cases (table 2).

In general the picture is that of an infant who is normal at birth and who does well for several months, then develops dyspnea, cough and intermittent cyanosis. Examination reveals cardiac enlargement, heart sounds of poor quality, either no murmur or a faint one, and signs of heart failure often with râles and enlargement of the liver. The ECG shows evidence of left ventricular hypertrophy in the precordial leads.

TABLE 3

RELATIVE FREQUENCY OF VARIOUS TYPES OF HEART DISEASE IN INFANTS AND CHILDREN AS SEEN AT AUTOPSY*

Most frequent gross congenital anomaly, complete transposition of great vessels	20
Mural endocardial fibrosis	15
Second most frequent gross congenital anomaly, tetralogy of Fallot	12
Idiopathic interstitial myocarditis	6
Left coronary artery arising from pulmonary artery	1
Glycogen storage disease of heart	0

* Data taken from 2,352 consecutive autopsies on infants and children done between 1935 and 1952 at the Children's Hospital of Buffalo, done by, or under supervision of one of the authors (K.T.). Anomalies of coronary arteries were searched for routinely. Chemical examination of cardiac muscle for abnormal amounts of glycogen was made whenever there was unexplained cardiac enlargement. Pathologic material and records of cases of mural endocardial fibrosis and idiopathic interstitial myocarditis were reviewed in detail for this paper.

Frequency

There are no reported data on the relative frequency of this condition as a cause of death. The records of the Children's Hospital of Buffalo indicate that it is one of the common causes of death from heart disease during infancy (table 3).

Differential Diagnosis

The following conditions should be considered in the differential diagnosis: gross malformations of the heart and great vessels, interstitial myocarditis, glycogen storage disease of the heart, vitamin deficiencies and rhabdomyoma.

Gross Malformations: Taken together, gross congenital anomalies of the heart and great vessels are undoubtedly the chief cause of cardiac enlargement during infancy. If only the conditions causing preponderant hypertrophy of the left ventricle are considered, many abnormalities can be excluded. The presence of palpable femoral pulsations practically eliminates the possibility of coarctation of the aorta. A patent ductus or an aortic septal defect are unlikely in the persistent absence of a loud basal murmur. The same holds for aortic and subaortic stenosis. The complex anomaly consisting of a rudimentary right ventricle, tricuspid atresia, pulmonic stenosis and associated septal defects can be differentiated both by persistent marked cyanosis and by the characteristic fluoroscopic findings.

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery: This abnormality typically produces marked hypertrophy of the left ventricle and clinical manifestations which are frequently similar to those found in infants suffering from endocardial fibrosis, the authors believe this is the most difficult differential diagnosis. Here again the chief help may come from the ECG for it may be that most of these cases will show an infarction pattern in the precordial leads. Unfortunately, in such cases the electrocardiographic studies with chest leads are inadequate and conclusions cannot be drawn. The tracings in Case 2 reported by McKinley, Andrews and Neill[28] show no significant differences from those reported here. However, Case 1 of the same series reveals electrocardiographic changes in the chest leads similar to those seen in coronary occlusion. Whether these two conditions can usually be differentiated by their electrocardiographic pattern remains to be determined.

It seems apparent that endocardial fibrosis is of much more common occurrence than aberrant left coronary artery arising from the pulmonary artery. No series larger than four of the latter condition has been reported. Yet Craig[5] was able to assemble 35 cases of mural endocardial fibrosis seen in two hospitals over a 20 year period. The marked difference in relative frequency of the two conditions at this hospital is shown in table 3.

Interstitial Myocarditis: Infants with idiopathic interstitial myocarditis and myocarditis produced by infections or toxic agents may frequently manifest clinical findings indistinguishable from those seen in infants suffering from endocardial fibrosis. However, the cardiac enlargement, when manifested in myocarditis, is nearly always due to dilatation of the chambers rather than to hypertrophy. Neither the comprehensive article of Saphir and his co-workers[29] nor the more recent one by Tedeschi and Stevenson[30] make any mention of either isolated or predominant left ventricular hypertrophy as a finding in cases of myocarditis. However, in the case of the 12 year old girl reported by Weber, Baldwin and Hall,[31] the left ventricle was found to be 14 mm. thick, the right 3 mm. Hence it is apparent that an occasional heart in this group may have sufficient preponderant left ventricular hypertrophy to show evidence of it in the ECG.

Glycogen Storage Disease of the Heart: The history and physical findings of infants dying of this rare disease do not differ significantly from those found in many cases of endocardial fibrosis. Di Sant'Agnese, Anderson, Mason and Bauman[32] in their very recent review of the 14 reported cases in the literature, found only three with accompanying ECGs. No chest leads were reported. Two of these tracings showed a normal axis, one left axis deviation. However, in six of these cases, the left ventricular wall was much thicker than the right. Whether such a preponderance will manifest itself in the precordial ECG remains to be proved, inasmuch as the increase in the weight of the heart and ventricular thickness is due to glycogen infiltration rather than to enlargement of the muscle fibers.

Di Sant'Agnese and his co-workers[32] point out the possibility of the clinical diagnosis of this condition by biopsy of striated muscle and histochemical demonstration of excessive glycogen deposition.

Once again the relative frequency of the two conditions should be of help in the differential diagnosis (table 3).

Vitamin Deficiences: Deficiency of both thiamine and ascorbic acid have been reported to cause cardiac enlargement during infancy. This enlargement is due to dilatation of the chambers with or without right ventricular hypertrophy.[33]

Rhabdomyoma: These congenital glycogenic tumors are described as being nodular and most frequently multiple.[34] There seems no reason to expect that they would give rise to evidence of left ventricular hypertrophy.

Summary

Evidence has been presented which indicates that endocardial fibrosis is a relatively common cause of death from heart disease in infancy and that a presumptive diagnosis of this condition can often be made during life. The salient features are: age under one year, marked dyspnea without persistent cyanosis, absence of a loud cardiac murmur on repeated examinations, enlargement of the heart, presence of femoral pulsations, and electrocardiographic evidence of left ventricular hypertrophy in the precordial leads. The chief conditions to be considered in the differential diagnosis are: aberrant coronary artery, interstitial myocarditis, and glycogen storage disease of the heart, all of which are much less frequent in the autopsy data. Four cases are presented in detail. In two of these the diagnosis was correctly made before death.

Note

Since this paper was submitted there have appeared two reports, both of which describe in detail the clinical findings in a number of proved cases of endocardial fibrosis. These reports discussed the differential diagnosis. Adams and Katz[35] presented one autopsied case with an accompanying precordial electrocardiogram. This tracing revealed evidence of left ventricular hypertrophy. Apparently on the basis of this one case these authors feel that evidence of left ventricular hypertrophy in the precordial leads will be the usual finding in cases of endocardial fibrosis.

Blumberg and Lyon[36] analyzed in detail the clinical manifestations in 94 proven cases (25 from their own files and 69 gathered from the literature) of endocardial fibrosis. They employed essentially the same criteria for selection of the cases as the present authors have here. Their conclusions regarding the age and the incidence of dyspnea, cyanosis, cardiac enlargement, and the presence of a significant murmur do not differ

materially from those presented above. However, they make no comment regarding the diagnostic value of the ECG in detecting anatomic left ventricular hypertrophy.

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SPANISH ABSTRACT

El Diagnóstico Clínico de Fibrosis Endocárdica
Revisión de la Literatura con Reporte de Cuatro Casos

Los autores relatan cuatro casos de fibrosis endocárdica en dos de los cuales hicieron el diagnóstico en vida por primera vez reportado y llevan a cabo una revisión de 94 casos en total para precisar el cuadro sintomatológico mas usual que facilite el diagnóstico durante la vida.

Los casos fueron seleccionados eliminando aquellos secundarios a coartación de la aorta y anomalías de las arterias coronarias, dividiéndolos en casos con y sin lesiones valvulares serias.

La mortalidad del padecimiento varía entre el nacimiento a los 8 años, con frecuencia mas alta entre 3 y 6 meses; 92% de muertes acaecieron durante el 1er. año de la vida. Disnea y tos fueron las manifestaciones mas frecuentes; 91%; la cianosis, aunque frecuente, estaba ausente, era intermitente o solo de caracter terminal, en el 72% de los casos; con excepción de los lactantes que murieron durante las primeras semanas de la vida, hubo solo un caso con cianosis persistente. No hubo soplos o solo suaves en el 79%, dato que correlacionado con ausencia de ataque valvular de significación en la autopsia, sube hasta el 95%. Se encontró, con cierta frecuencia también, fiebre, irritabilidad, retardo en el crecimiento o pérdida de peso, anorexia y dificultades en la alimentación y vómitos.

El 94% de los casos estudiados radiológicamente presentaron cardiomegalia, siendo marcada y de las cuatro camaras en los 4 casos que reportan.

No se encontró un trazo electrocardiográfico específico en los 23 casos en que se estudio, excepción de los 4 casos descritos por ellos, en los que sí se hicieron registros electrocardiográficos precordiales.

En el 72% de los casos estudiados en forma adecuada se encontró hipertrofia ventricular izquierda solitaria o de ambos ventrículos pero siendo de mayor grado la del izquierdo, por consiguiente, con registros precordiales múltiples la mayoría de los casos hubieran presentado los cambios electrocardiográficos respectivos.

En general el cuadro es el de un lactante normal al nacimiento que permanece bien por algunos meses hasta que comienza con disnea, tos, cianosis intermitente y al examen se encuentra crecimiento cardiaco, tonos algo apagados, sin soplo o uno suave, y signos de insuficiencia cardiaca, a menudo con estertores y hepatomegalia. El electrocardiograma muestra hipertrofia ventricular izquierda en las derivaciones precordiales.

Los autores piensan que debe hacerse diagnóstico diferencial con las malformaciones gruesas del corazón y grandes vasos, miocarditis intersticial, enfermedad glicogénica del corazón, avitaminosis y rabdomioma. Creen que es factible diferenciar el padecimiento de aquellas malformaciones que producen hipertrofia ventricular izquierda preponderantemente como coartación de la aorta, (presencia de pulso femoral), persistencia del conducto arteriovenoso o defecto septal aórtico, estenosis aórtica y subaórtica (ausencia de soplo basal intenso). Las malformaciones complejas con ventrículo derecho rudimentario, atresia tricuspídea, estenosis pulmonar y defectos septales asociados pueden diferenciarse por la cianosis marcada persistente y por los datos fluoroscópicos característicos. El diagnóstico diferencial mas difícil y que electrocardiográficamente no ha sido determinado es el origen anómalo de la arteria coronaria izquierda en la arteria pulmonar, que produce típicamente hipertrofia ventricular izquierda y manifestaciones clínicas que frecuentemente son similares a las encontradas en lactantes que tienen fibrosis endocárdica. Este padecimiento aparentemente es mas frecuente que la anomalía de la coronaria izquierda.

En la miocarditis intersticial idiopática o las producidas por agentes tóxicos o infecciosos, aunque

el cuadro clínico sea indistingible del de la fibrosis endocárdica, el crecimiento cardiaco, cuando se presenta, casi siempre es debido a dilatación de las cavidades mas bien que a hipertrofia y en la literatura actual no se hace mención de hipertrofia ventricular izquierda predominante o solitaria en casos de miocarditis, con excepción de un solo caso.

La diferenciación con la enfermedad glicogénica del corazón dependerá fundamentalmente, ya que tienen signos y síntomas similares, de que el electrocardiograma precordial registre o no, el aumento de espesor de la pared ventricular que en algunos casos existe predominando en el ventrículo izquierdo, ya que este aumento es debido a infiltración de glicógeno mas bien que crecimiento de las fibras musculares, y que por el momento no se ha investigado. Ademas, debe realizarse la biopsia de músculo estriado para eliminar la presencia excesiva de glicógeno y tener en cuenta la mayor frecuencia de la fibrosis endocárdica.

En las deficiencias de tiamina y ácido ascórbico la cardiomegalia es debida a dilatación de las cámaras con o sin hipertrofia ventricular derecha y en el rhabdomioma no existe razón para esperar que se formen tumores que determinen hipertrofia ventricular izquierda.

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

ANTIBIOTICS

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HAROLD WEATHERMAN, M.D., San Diego, Calif., and
WALTER C. MCKEE, M.D., Chicago, *Secretaries*

Chairman Neter: The advances made in the treatment of infectious diseases since 1935, and more particularly during the last decade, have been nothing short of miraculous. Surveying these accomplishments briefly, it is clear that adequate chemotherapeutic and antibiotic agents are available for many bacterial and rickettsial infections and even for a few diseases caused by the larger viruses, closely related to the rickettsiae. Furthermore, the medical profession has had available for many years drugs which have proved effective in maladies caused by some protozoa, such as malaria, and substantial further advances have been made in this field during the following World War II.

At the same time, we are all painfully aware that in the daily practice of pediatrics we are still lacking chemotherapeutic and antibiotic agents which are curative in diseases caused by the true viruses and, to a larger extent, in illnesses due to fungi. Also for certain bacterial infections, such as those caused by mycobacteria, Proteus, Pseudomonas and others, the ideal antibiotic will yet have to be discovered. Indubitably, the research that is going on throughout the civilized world in the search for newer and better antibiotics will, in due time, solve these all-important problems.

The field of antibiotic therapy and prophylaxis has expanded at such an extraordinary rate that it has not yet been possible in all instances to determine with certainty the relative efficacy of various antibiotics in all infections and the optimal dosage schedule for each. It is quite likely that all of us, for example, use more penicillin in some patients than is needed.

Antibiotic therapy may result in certain undesirable side reactions, some of which may not become evident from the study of the first 100, 1,000 or even 10,000 patients. This has become painfully clear in the case of chloramphenicol. Furthermore, we have witnessed recently that antibiotic therapy may bring forth changes in the normal bacterial flora of the human body and that these changes in turn may result in certain undesirable side effects, such as the development of superinfections, the emergence of a different and potentially pathogenic resident bacterial flora, and vitamin deficiency. Unfortunately, also, emergence of antibiotic-resistant bacteria may follow the use of certain antibiotics, particularly streptomycin. That this problem is of major significance in the specific therapy of tuberculosis cannot be doubted.

We also have become aware of the fact that the combination of 2, 3 and even 4 antibiotics does not always result in proportionate increases in efficacy and, indeed, there is adequate laboratory and

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even some clinical evidence to the effect that the combination of 2 drugs in certain dosages, in infections by certain micro-organisms and under certain conditions may result in antagonistic effects. On the other hand, it has been established beyond doubt that the emergence of a resistant micro-organism, such as resistant tubercle bacilli, may be definitely delayed by the simultaneous use of a second antimicrobial agent.

As yet we do not have available a rapid, simple and entirely reliable laboratory method to determine *in vitro* what a given antibiotic will accomplish in our patients. Some investigators seem to be satisfied with the widely used disc method for antibiotic sensitivity determination, but others consider more complicated methods essential. Beyond this, discrepancies between *in vitro* and *in vivo* or clinical results have to be expected, if one considers the numerous differences which exist between media and tissues, the distribution of the antibiotic and many other factors.

There are so many accomplishments and so many unsolved problems at this time in the field of antibiotic therapy that it will not be difficult to discuss this subject for 3 hours. Perhaps it may be wise to take up the various ramifications of antibiotics in the following order.

1. The selection, modes of administration, dosage schedule of antibiotics in various infections of children and the results of antibiotic therapy.
2. The question of synergism and antagonism of antibiotics.
3. The problem of development of resistance to antibiotics.
4. The laboratory aspects of antibiotic therapy.
5. Finally, the side effects of antibiotic therapy, namely, the toxic reactions, the allergic reactions, the emergence of a different microbial flora, hormesis or growth promotion by antibiotics, and Herxheimer reactions.

We would like to make this Round Table as informal as possible and cordially invite each and every one to participate in the discussion and to relate the results of personal observations and investigations.

Dr. Lepper: Our first topic is selection of antibiotics and mode of administration. Obviously the selection of antibiotics at the present time is to a certain extent a matter of personal opinion rather than scientific information. We have had in the last few years a rapid increase in the number of agents available, and in some situations there are just not enough patients to do controlled studies to obtain an accurate comparison. Therefore the testing of a new antibiotic in certain diseases is a matter of trying it on a few cases and if you have a disappointing result the agent is discontinued but if the results are favorable no true comparison is made with results obtained with other agents. In many places the information is rather scanty.

You are all aware that the last great influx of new antibiotics are the agents chloramphenicol, terramycin and aureomycin. For convenience we will lump these 3 together to save repeating the individual ones over and over again. We usually approach this problem of setting up the antibiotics from the point of view of the etiologic agent involved. Dr. Neter has mentioned the viruses and the fungi where we have practically nothing to offer in the way of antibiotic therapy.

There is a group of larger viruses that are on the borderline between rickettsia and viruses, such as the lymphogranuloma virus, where the antibiotics have some activity. In this group, penicillin has some slight activity in the laboratory but never was a good agent therapeutically. Here the 3 new antibiotics are recommended and the results are moderately gratifying.

The next large group of organisms are the rickettsiae themselves. We have 3 agents, apparently of equal worth, since one has not seen any convincing evidence that any of the 3 new antibiotics is preferable to the other. The results have been quite satisfactory, even life saving, in Rocky Mountain spotty fever, typhus and Scrub typhus.

In the bacterial group of infections we start with the coccal infections. The coccal infections have for the most part been a fairly well solved problem with a few exceptions. Penicillin is still the drug of choice in coccal infections. Staphylococcic infections are indeed our most serious problem at the present time in the coccal field from the point of view of numbers of resistant infections. The staphylococcus is the only organism which was originally sensitive and has shown a pattern of becoming predominantly resistant to penicillin. It is certainly true at the present time that in the different communities, anywhere from 30 to 80% of staphylococci are penicillin-resistant. Year after year we are finding that the percentage of resistant organisms is increasing. The number of organisms even partially sensitive to penicillin, ones which could be treated with large doses, is decreasing all the time. It is becoming quite a problem in management. Almost all the other

antibiotics have some effect against staphylococci. Sulfonamides never had a really good effect against staphylococci and the problem of sulfonamide resistant organism was very real before penicillin and it still is a problem.

Streptomycin has a fair amount of antibacterial action for staphylococci. Again here we have rapid development of resistance to streptomycin as we do with almost all rapidly growing organisms.

Many staphylococci are quite sensitive to aureomycin; there were a fair number of intermediate sensitivity and relatively few that were highly resistant.

When terramycin first came out staphylococci fell into 2 groups, one in which the organisms were quite sensitive and a second where they were rather resistant. Here again there has been a shift from the sensitive to the more resistant forms.

Chloramphenicol did not have very many real sensitive forms; there was a moderately sensitive and a rather resistant group. There are still patients who will respond to chloramphenicol better than the other antibiotics.

Bacitracin is the other agent we have for serious staphyloccic infection and, in fact, it is the only place we use this agent. I doubt whether it would be on the market had it not been for resistant staphylococcic infections. This agent may be helpful in many of the serious infections. Here the problem of development of resistance has not been as rapid because the drug is not as widely used although the organism can certainly become resistant to the agent.

The beta hemolytic streptococcal infections, particularly groups A- C-G, have presented no problems since penicillin was introduced nor is there any real evidence that they are going to present a problem at the present time. While the other agents work moderately well in streptococcal infections they certainly do not eradicate the organism as well in the culture. More relapses occur and one feels that the best agent in this particular group is still penicillin.

The other streptococcal infections: some alpha-hemolytic and nonhemolytic streptococci, particularly the enterococci, have been quite a problem. Many of the alpha-hemolytic streptococci have been quite susceptible to penicillin and they seem to be remaining so. In addition, we find they respond well to a combination of penicillin-streptomycin in endocarditis. The enterococci, on the other hand, have been recalcitant from the beginning. They never were too susceptible to penicillin and there is no good evidence they are becoming more resistant. This is also true of the new antibiotics. Our major failures in endocarditis are infections with enterococci. Infection with these organisms constitutes another field where a combination has been explored fairly successfully, simply because they haven't responded too well to any single antibiotic.

In pneumococci infections, penicillin is most effective although all 3 new antibiotics work well. We can do very well with large doses of penicillin in pneumococci meningitis.

It is true in the salmonella infections, as exemplified by typhoid fever that chloramphenicol works better than the others. In the other gram-negative rod infections, the 3 new antibiotics seem to be equally effective.

You may have noticed that we haven't said much about streptomycin! Streptomycin has been pretty well replaced but there are certain situations where it is useful in the gram-negative field. Two important organisms in the gram-negative field which have become major problems are the Pseudomonas and Proteus. Pseudomonae are quite resistant to the new antibiotics as well as to penicillin but these organisms frequently occur as superinfections. This is true in the urinary tract, in the bronchial diseases and in some cases of pneumonia, such as that in poliomyelitis patients following tracheotomy. These have been particularly hard to treat and one can't give a blanket answer. A streptomycin sulfonamide combination may work or polymyxin may be used.

For the spirochetal infections, penicillin still stands prominent in the treatment of syphilis, although the newer antibiotics have some activity.

In the fungal infections we have very little in the way of antibiotics. We have skipped tuberculosis because it is a problem unto itself. We do have a wealth of data on the combination of streptomycin and PAS which is the standard therapy and against that we have to compare the new compound isoniozide. Among the tuberculosis problems which usually confront pediatricians, there is at the present time data accumulating on tuberculosis-meningitis and miliary tuberculosis where isonizide appears to exert a favorable influence. On the problem of the progressive primary there is not as much data available on the relative merits of isonizide either with or without streptomycin compared to what one can accomplish with streptomycin and PAS.

This outlines the field for the first portion of this program and we certainly would appreciate discussion from the floor to take up problems in more detail.

Question: Did you say that bacitracin is available other than for local administration?

Dr. Lepper: Yes, there is a systemic form of bacitracin that is marketed for intramuscular use which is probably indicated in certain staphylococcic infections, for example, in certain cases of osteomyelitis which are failing to respond to other antibiotics. With the drug we limit the dose to a maximum of 200,000 units a day or 3,000 units/kg./24 hours. If you get above that you are getting in a range in which you may get actual damage to the kidneys. We have seen a patient with staphylococcal meningitis with continued positive cultures on penicillin and other antibiotics which did clear up on bacitracin but not intramuscular alone—it took intrathecal in addition.

Dr. John E. Brown, Jr., Columbus, Ohio: There has been a tendency for people to include preparations of polymyxin, neomycin and comparable preparations in various skin ointments that are used for staphylodermia. Do you see any object in having the compound preparation used in the average case? Would they cause a systemic sensitivity if you had to use the drug systemically later on?

Dr. Lepper: The idea of this combination is that you can prevent a superinfection. I don't believe it is likely that one will ever prevent superinfection of the skin by any combination of antibiotics. It is much better to try to treat the organisms you have at hand and hope that if you eradicate that, you will be able to control the infection. I am not much in favor of combination ointments or combinations of any kind except where they have been very well studied. As far as the problem of ointments is concerned we feel that bacitracin should not be used too widely for minor skin infections, in the hope that the development of large numbers of resistant bacteria may be minimized.

Chairman Neter: The same tendency can be noted in regard to intestinal infections. Combinations of 2 or 3 drugs—one active against cocci, the other against gram-negative bacilli—have been recommended for local intestinal therapy and prophylaxis. Antibiotics which are but poorly adsorbed from the gastrointestinal tract may be without major toxicity when given by mouth. There is another aspect connected with the problem of superinfections. One must recognize the danger of exposure to potentially pathogenic micro-organisms which may be far more predominant in a hospital ward than elsewhere. For example, we have seen the emergence in the respiratory tract and even on the skin of numerous Pseudomonas (B. pyocyaneus) organisms in infants and children receiving certain antibiotics and it is not difficult to visualize that such micro-organisms may be transferred to other patients who are under treatment for a given infection with an antibiotic that may be totally ineffectual against Pseudomonas. Under certain circumstances, including prematurity, ACTH or cortisone therapy and others, the Pseudomonas may become responsible for superinfection that on occasion proves to be fatal.

New Speaker: You spoke of penicillin being the preferable drug for the treatment of spirochetal infections such as syphilis. I have a patient 8 years of age who was treated by a competent physician as a very small infant for congenital syphilis with penicillin, with reversal of the serology. He was sent in to me by an ophthalmologist because of an interstitial keratitis. He still has a consistently negative serology. Is there any way illuminating toward the possibility that it might be a better idea to also treat patients who have congenital syphilis with the arsenic compound or does that particular picture I described to you make any sense at all? Should I continue with any more penicillin?

Chairman Neter: Can you be sure that keratitis is syphilitic in origin?

First Speaker: So far as we know, sir. The tuberculin reaction is negative, complete x-ray of his teeth and sinuses show no possible cause for the interstitial keratitis and it is a typical picture. As a matter of fact, before I knew about this patient being treated during the war when I was away, I sent the patient back to the ophthalmologist saying I could find no evidence of syphilis and would he please tell me if he felt there might be other causes. The ophthalmologist said he didn't care what the serology was—it is syphilitic keratitis! I firmly believe it is.

Dr. Lepper: Was the serology quantitative? There are 2 problems there: is it syphilitic and how frequently do you get keratitis without positive serology and if this is syphilis how frequent are relapses with negative serology? Certainly relapses occur with positive serology but most of the time the serology relapses before the patient relapses. The problem then is how best to prevent relapse. If you assume this is syphilis then you have to assume it is a syphilitic relapse with a negative serology which would be something difficult to explain but I suppose it can happen. Then it would be a case of the frequency of relapses and there are fairly definite data on relapses. There are not many good studies on congenital syphilis, perhaps the follow-up is not great enough. In adult syphilis the relapse rate is about 15%. Many of the relapses on retreatment will improve.

As far as the treatment of this individual is concerned, certainly one should try another course

of penicillin or one of the other antibiotics. Some of the patients who have relapsed on penicillin have responded very well to penicillin or another antibiotic. Aureomycin has had more study than the others and is probably the drug of second choice.

Dr. Martin A. Quirk, Red Bank, N.J.: I would like to ask your opinion of the therapy of penicillin by mouth in rheumatic fever?

Chairman Neter: Several problems are entailed in this question. 1. Penicillin therapy during active rheumatic fever does not affect the course of the rheumatic process. The antibiotic should be used if rheumatic fever is associated with signs and symptoms of streptococcal infection or for the eradication of the carrier state. 2. Penicillin has proved to be of extraordinary value in the prevention of rheumatic fever. Either when administered prophylactically to prevent streptococcal infection or when used within a day or two after the onset of streptococcosis. For prophylactic purposes penicillin can be given by mouth; in a study with Dr. E. C. Lambert and Dr. W. S. Webster, we are using 200,000 units twice a day. If penicillin is used for therapeutic purposes it may be given parenterally or by mouth in a dosage of 1,000,000 units a day. Recently we observed a subject who continuously carried group A hemolytic streptococci in the throat in spite of administration both by mouth and by injection of adequate amounts of penicillin and who lost the hemolytic streptococci following oral administration of erythromycin.

New Speaker: I have had the experience of giving my patients oral therapy and having them develop diarrhea. The same child getting intramuscular injection does not get diarrhea. Is it because you are interrupting the flora?

Dr. Lepper: We know very little short about the mechanism of diarrhea from any of the antibiotics. We presume with the new ones it is an irritative phenomena and with penicillin certainly loose stools may occur almost from the first dose so flora alterations do not seem likely. Some of the serious diarrheas are probably flora alterations.

Chairman Neter: We have had some unhappy experiences in Buffalo. During or following the use for prophylactic purposes of several antibiotics, 8 patients developed severe and, in some cases, fatal enteritis. The studies by our pathologist, Dr. K. L. Terplan, leave but little doubt that this lesion was associated with and probably caused by staphylococcus. Such experiences should make us rather cautious in using antibiotics without proper indication.

Dr. Harold W. Dargeon, New York City: In a burn case with extensive involvement that has a positive skin culture and blood culture of Ps. aeruginosa, would you use polymyxin?

Dr. Lepper: Whether I would choose polymyxin first would depend a lot on the urgency of the situation. Polymyxin is relatively toxic as we know; in addition, a burned patient is also apt to have a certain degree of kidney damage pre-existing so one is in a rather hazardous situation. Certainly if it is felt that there is time, I personally would prefer, when laboratory results indicate that streptomycin may be effective, to try a combination of streptomycin and the sulfonamides first. If there is urgency, I would use polymyxin if there is not time to find out about streptomycin.

Chairman Neter: Recently a study on a large number of burn cases was published from Great Britain indicating that polymyxin gave the most satisfactory result in preventing infection with B. pyocyaneus. Since the patient referred to in the question also had a positive blood culture, it is important to emphasize that *in vitro* determination of the sensitivity of the strain should be carried out as a guide to antibiotic therapy. Such determinations are unnecessary when a given microorganism, such as the pneumococcus, is invariably sensitive to a given antibiotic, such as penicillin. On the other hand, such tests are of real value when one is dealing with a species of bacteria characterized by marked variations in susceptibility to various antibiotics of different strains. For example, recently we observed a patient with meningitis due to B. pyocyaneus; the strain was markedly sensitive *in vitro* to aureomycin and the patient recovered following the use of this antibiotic.

Dr. Lepper: The most important thing about sensitivity is that it be done accurately regardless of the method used.

Dr. John F. Miller, Newark, Ohio: Of the 2 methods of handling a prophylaxis of rheumatic fever, (a) giving a day-after-day treatment of penicillin by mouth and (b) treating vigorously and immediately any respiratory infection or sore throat that shows up, what is the preference in handling the disease?

Chairman Neter: Indubitably, continued penicillin prophylaxis is better than vigorous and immediate treatment of an upper respiratory infection, since a fair number of streptococcal infections

are subclinical in nature and hence would not be recognized and treated and yet may initiate another attack of rheumatic fever. Furthermore, if treatment were started after a lapse of a few days, rheumatic fever may not be prevented.

Dr. Lepper: If you have one strep infection in the family the other members should certainly be studied for streptococcal infection by throat culture. If the throat culture is positive they probably should be treated to eradicate the organism. It certainly is true that people can get antibody responses to positive throat cultures with a minimum of symptoms. They also get rheumatic fever from this low grade infection.

Question: Do you start your prophylaxis during the acute attack of rheumatic fever?

Dr. Lepper: Yes, particularly if the individual is in the open ward type of hospital where there are other streptococcal infections.

Chairman Neter: The point made by Dr. Lepper regarding streptococcal infection could be made also with respect to epidemic meningitis. An effort should be made to eliminate the meningococci from the individual(s) who served as the source of infection. It is tragic to see a second child of a family develop and even die from meningococcal infection, because appropriate measures were not taken to eliminate the source.

Question: What about scarlet fever?

Chairman Neter: Today scarlet fever is no more and no less than a streptococcal infection of like severity and should be treated accordingly. To my mind, with scarlet fever being relatively mild at this time and in this part of the world, active immunization against this malady is no longer indicated, even in nurses.

Dr. Lepper: The problem of treating them in the home is the dust problem. The streptococcus is a very resistant organism as far as getting it out of an environment. It persists in dust for some time.

Dr. Hugh C. Thompson, Tucson, Ariz.: From the viewpoint of prophylaxis I would like to point out that we all treat in the home many infections which we don't diagnose bacteriologically. Therefore, I am sure they are streptococcus. You get scarlet fever, you do know it is streptococcic—would it be worth while for me to give antibiotics prophylactically?

Chairman Neter: If you were to restrict penicillin prophylaxis to only those families with one of scarlet fever, you would use this regime in only a minor fraction of individuals exposed to streptococcus. I very much doubt whether penicillin or another antibiotic should be given every member of every family with one individual having an infection of the upper respiratory tract or even when a bacteriologically proved streptococcal infection is found. Family contacts should be observed carefully and treated when clinical infection develops. On the other hand, as was pointed out before this prophylaxis should be carried out in special instances, for instance, in susceptibles to rheumatic fever. Should we experience an outbreak of malignant scarlet fever, as it was present in Europe in the late twenties, prophylaxis with penicillin of exposed individuals may become advisable.

Dr. Lepper: We will now consider the effect of the mycins in whooping cough. There seems to be a fairly definite effect of the newer drugs on whooping cough. This effect is not measured in terms of hours. One of the best studies was done on a large group of whooping cough patients with the 3 mycins and penicillin in comparison (Hazen, L. N., and others, J. Pediat. **39**:1, 1951). It was found that the cultures do become negative sooner. It was also felt that the paroxysms are decreased in pertussis with the antibiotics. Moreover if you do an incidental observation of pertussis such as we did in our hospital without controls, one is not impressed by the rapidity of the disappearance of the paroxysmal stage. What did impress us was that good isolation technic helps to prevent superinfection and you can practically eliminate the occurrence of pneumonia. Only one patient among 400 to 500 pertussis patients treated in the past 3 years developed pneumonia. This occurred shortly following discontinuance of antibiotics in the hospital. This control of pneumonia, otitis media and other complications is a very real gain and we feel pertussis patients should be treated but the drugs are not a panacea. We have had several patients who have received chloramphenicol or aureomycin throughout the entire incubation period and yet have developed pertussis. On the other hand, certainly the course of the disease is much milder if you control a secondary infection.

Chairman Neter: Regarding the preference of one penicillin preparation from one company over another one from a different source, the physician is well advised to study graphs in advertisements rather carefully. A graph may suggest a high and prolonged level, but study of the scale may reveal that the highest level reached is not 0.8 units cc. blood but only 0.09 units cc. Such a difference

may be of greater significance in the management of severe infections. Furthermore, such curves are computed on the basis of tests on a number of subjects and the physician should have available data regarding the variations in penicillin levels in different individuals. As in the early days of chemotherapy, when arsphenamine, for example, was administered only every few days, we realize at this time that a continuous effective level is not necessarily superior to intermittent effective levels. In fact, with antibiotics which exert their main effect upon multiplying bacterial cells, the latter form of therapy may be superior to the former.

Dr. Lepper: The thing to remember about long active preparations is that you do not get high level the first day; you don't get much above the minimum requirement. One would judge that with most streptococci you ought to have a level at least .05 units/cc. In addition one must know what is meant when an average level of 0.03 units/cc. is recorded. It may mean that 50% of the people had no demonstrable activity whereas the other 50% had 0.03 to 0.25. You have to know what the reliability is as well as the average level. That is extremely important. If you try to add up increments with long acting preparations to a fairly high serum level in an infection that has a localization in which penetration is difficult, a preparation which gives a fairly high initial level should be used, for example, an aqueous suspension of procaine penicillin which frequently gives levels of 1 or 2 units/cc. at its peak. If you add that together every 6 hours you can get levels of 5 to 10 units/cc. This will penetrate into almost anything including the spinal fluid. On the other hand, if you use a good procaine penicillin in oil and aluminum monostearate preparation which gives a peak level of about 0.25 you get only 1 or 2 units/cc.

If in treating, for example, pneumococci meningitis when you are past the first couple of days, the real acute stage, you want to reduce the number of injections a long acting preparation such as an aqueous suspension of procaine penicillin will work. Ordinarily we start about the 2nd or 3rd day overlapping with the soluble salt. Thus we build up a good repository level before we stop the soluble penicillin and at that point one can change over quite nicely.

Chairman Neter: The question may be raised as to whether a penicillin preparation which produces demonstrable blood levels over a period of 2 weeks may not have one disadvantage, namely, its prolonged presence in a penicillin-sensitive individual. Obviously, it would be desirable in such a patient to have the penicillin excreted more rapidly.

Dr. Lepper: Time alone will have to answer that question of the allergenic difficulties of long acting preparations. Actually one is hard put with penicillin to get a theoretic answer in that we may give an endocarditis patient who has developed urticaria in the second week of therapy continuous penicillin and the urticaria may clear up. On the other hand, we have another group of patients who have not had the drug for 14 days at which time they developed a self-limited type of serum sickness which one couldn't reproduce by giving penicillin again. So one doesn't know how much the presence of penicillin per se will contribute to the reactions.

Dr. Edgar L. Clayton, Springfield, Mo.: Would you mention something about the problem of bacteriology diagnosis when the patient has already had antibiotics before entering the hospital.

Chairman Neter: Indubitably, this is a real problem at the present time. If an effectively antibiotic has been used, it may be impossible to demonstrate the etiologic agent by cultural methods. Needless to say, efforts should be made to neutralize the antibiotic in the sample, for instance, penicillin by the addition of penicillinase. In some diseases the etiologic diagnosis may be made by the demonstration of a rise in specific antibodies. This method has proved valuable to us in cases of meningococcal meningitis. On the other hand, it cannot be emphasized too strongly that, even when a child had received antibiotics or sulfonamides, bacteriologic examinations should not be withheld because of that fact alone. It is frequently possible to demonstrate the pathogen by cultural means even in such cases and thus aid the clinician in further management. Furthermore, such examinations are imperative in patients who do not respond to therapy as expected, since either the organism may have become resistant or superinfection may have taken place. In both cases, the isolation and study of the etiologic agent should not present real difficulties.

Dr. Lepper: Make it a point to get all the information you can about the original therapy and then take a culture as though it were a fresh case. As far as your immediate change in therapy—if an immediate change is indicated one can only treat according to probability. That is, if we get a patient with meningitis who has been getting 600,000 units of penicillin a day and we can't find an organism on the original smear—what are we going to do while we are waiting for the cultures? In such situations one must make the best possible clinical diagnosis and treat accordingly.

If it is a problem of a possible superinfection then you can start over with fresh cultures. If the

patient has no valid indication for continuing the antibiotic, stop it until you find out what he has. At the present time there is a reluctance to stop antibiotics that is too great. Unless the patient is critically ill, it is better to stop the antibiotic for a few hours and see if you get back to bed rock. It is hard to do this with a long active preparation.

Dr. Francis W. Helfrick, Manchester, Conn.: Is there any simple test one can do to determine penicillin sensitivity? That is, when there is some question as to previous reaction, can you test for that?

Dr. Lepper: I know of no simple test; sometimes we have positive skin tests but they are the exception rather than the rule. At the present time there is no real sure test for people with a hypersensitivity.

Chairman Neter: The pediatrician may keep in mind that some patients who are allergic to penicillin G may not be sensitive to penicillin O. Recently we observed a patient with complicated mastoiditis who tolerated penicillin O but not penicillin G.

Dr. Martin A. Quirk, Red Bank, N.J.: If we have a case of known H. influenzae meningitis, would we be justified, in view of all the work that has been done with chloramphenicol, in using that drug or should we use aureomycin?

Dr. Lepper: Our results with aureomycin alone are as good as those reported with chloramphenicol alone or in combination. We feel that if you diagnose influenzae bacillus meningitis and get it treated within any reasonable length of time you are going to need startling results with chloramphenicol to be better off than you are with aureomycin.

At the present time you are justified in starting off with terramycin or aureomycin. You should always give the drugs parenterally the first day or so.

Chairman Neter: We have used, at the Buffalo Children's Hospital, chloramphenicol extensively in the treatment of meningitis due to H. influenzae, with rather gratifying results. Among 71 consecutive cases, including infants and children who received this antibiotic as the main chemotherapeutic agent, there was only one fatality (fatality rate of less than 2%). In none of the many patients treated at this hospital with chloramphenicol, including over 100 who were given the drug by the intramuscular route did this treatment result in blood dyscrasia. It must be realized that this complication has occurred in only approximately 200 out of an estimated 8,000,000 persons and we do not yet know the reason why this unfortunate sequela happens in one individual and not in many others. However, with this information on hand, one will use chloramphenicol only in serious conditions in which this antibiotic is superior to others.

Question: What is optimal therapy in treating the viruses?

Dr. Lepper: There has been no real success in treating virus infections except for those in the lymphogranuloma-psitticosis group and primary atypical pneumonia, if that is a viral disease. In these situations, one of the broad-spectrum drugs should be used.

I should like to take this opportunity to discuss the concept of "optimal" therapy. To decide what is optimal therapy is a difficult thing to do. You can take any drug, we did it with the sulfonamides, in pneumococcus pneumonia, or in meningitis and find that there are some patients who get well on a dose that is considered suboptimal. The difference one can get from the maximum antibiotic effectiveness on one hand and no antibiotics on the other hand is different for each disease. At suboptimal doses, the effect will lie between these 2 extremes but some effect will generally be seen. Antibiotic therapy is not an all or none phenomenon.

There will be a good many infections of a less serious nature such as Str. beta hemolytic infections, pneumococcic infections in the lung, where you will be able to treat with many agents and see many recoveries. Now that doesn't mean that the results will be equally good if you collect enough patients. They may or may not be and that has to be established for each disease and each new agent before stating that something is optimal. All one can say is that a given drug is satisfactory in a certain percentage of patients at a given dose. For the more serious infections that are seen infrequently, it is necessary to have controlled studies done as rapidly as possible to determine optimal therapy.

Dr. Lepper: As far as the treatment with oral bacillin is concerned, certainly oral therapy is good therapy providing you use a large enough dose. The point is that oral therapy is never as reliable in any situation as parenteral therapy. We all know that the gastrointestinal tract is not infallible and particularly when you have the possibility of vomiting. If a person seems quite ill, it is not wise to trust the oral route.

Unfortunately, with the newer antibiotics, particularly terramycin and aureomycin, intravenous medication gets to be a hospital procedure. On the other hand, it is the only parenteral route you have for these compounds.

The toxicity of the compound makes a tremendous difference in what you do with a dose schedule. Penicillin is very low in toxicity. Having a low toxicity means we can increase the dose a great deal and in so doing, we have a wide range of things that can be treated which are not treated by the ordinary dose. Wherever we have a penetration problem or relatively resistant organisms that are still sensitive enough that satisfactory levels can be obtained, large doses can be given.

Drug reactions are more of an adult problem and that is certainly true of the sulfonamides. The same is also true with penicillin.

Dr. Julius Margolis, Coatesville, Pa.: What is the relative value of sulfadiazine as compared to penicillin in the prophylaxis of rheumatic fever?

Chairman Neter: Both sulfadiazine or similar sulfonamides and penicillin are efficacious in the prevention of streptococcal infection and thus of rheumatic fever. In the study now in progress in Buffalo, N.Y., in cooperation with Dr. E. C. Lambert and Dr. W. S. Webster, we are finding penicillin (2 times 200,000 units by mouth) superior to sulfadiazine. It cannot be stressed enough that, depending upon the location, this prophylaxis may have to be carried out throughout the year, even including the summer months. It may also be pointed out that individuals susceptible to rheumatic fever should be freed of hemolytic streptococci first, before the prophylactic program is initiated.

Question: In general, are antibiotics bacteriostatic or bactericidal?

Chairman Neter: Of the clinically available antibiotics some, such as penicillin, streptomycin, bacitracin and polymyxin, are bactericidal and others, for example, aureomycin, terramycin, chloramphenicol and, in all likelihood, magnamycin and erythromycin are essentially bacteriostatic. It is important for the clinician to realize that even a bacteriostatic drug, which stops multiplication of the micro-organism, may bring forth elimination of the pathogen, which either succumbs or is eliminated by the defense mechanisms of the patient, such as phagocytosis and antibodies.

Dr. Paul W. Beaven, Rochester, N. Y.: Do you give penicillin by mouth with food in the stomach?

Chairman Neter: We prefer to give penicillin approximately 30 to 60 minutes before meals, although it may be given also with or following food.

Question: Should we prescribe chloramphenicol in view of the fact that the new Red Book says it very definitely should not be used?

Dr. Lepper: It, has, unfortunately, been shown to cause aplastic anemia and almost all patients have ended fatally once this has developed. It means there is a definite toxicity that wasn't appreciated until the last year or year and a half at the earliest. Nevertheless, the number of bona fide cases is few so that the total incidence of reactions have been quite low.

Therefore, if you have an infection where chloramphenicol is appreciably better than any other therapy, as in typhoid fever, perhaps, it would be the thing to use. Some people feel that chloramphenicol is the best drug in influenzae bacillus meningitis. We do not feel that this is established and are now doing an alternate case study. If it is concluded to be the best drug here, its advantages may again outweigh the toxicity. The use of chloramphenicol at the present time should be limited to those situations where you have a serious infection which seems to be benefited more by chloramphenicol than by streptomycin or the other agents.

Dr. Lepper: One of the biggest gains in the last year in antibiotics has been the further elaboration of the problem of superinfection. I would like to emphasize certain points. One is that we use relatively few adrenal hormones in hyperacute infections. We, too, have seen in older children acute Pseudomonas sepsis following the antibiotic combinations plus cortisone.

Question: How soon after the administration of terramycin will diarrhea develop?

Dr. Lepper: We try to differentiate mechanism in diarrhea in that irritation from the antibiotic usually begins almost immediately and usually has some vomiting associated with it. In the diarrhea that starts about the third day and usually persists following the discontinuing of the antibiotic, one can strongly suspect a superinfection. Careful study of the stool is most important.

Chairman Neter: In view of the fact that monilial and staphylococcal infections of the intestine may occasionally follow antibiotic therapy, it should be stressed that for bacteriologic examination fecal specimens should be seeded not exclusively on culture media which support the growth of gram-negative bacilli only, such as Endo, MacConkey and SS agar, but also on blood agar and Sabouraud agar. Furthermore, it is helpful to examine such specimens microscopically for the

presence of various bacteria and leukocytes; such a procedure may give the bacteriologist not only an idea of the type of micro-organism present but also affords him an opportunity to estimate quantitatively the proportion of various bacteria and may suggest the use of additional culture media for specific purposes.

Question: What are the recommended doses on a per kilo basis of both aureomycin and terramycin?

Chairman Neter: In children, aureomycin and terramycin may be used in amounts of 10 to 50 mg./kg./24 hours, depending upon the severity of the infection and the susceptibility of the etiologic agent. In some infants we have used as much as 500 mg./kg./24 hours.

Dr. Clarence H. Webb, Shreveport, La.: I would like to have you mention the relationship of dosage and duration of treatment on the emergence of undesirable infections—the use of aureomycin in fibrocystic disease, for example, and short term therapy with large doses.

Chairman Neter: The problem of the emergence of an undesirable bacterial flora following the use of antibiotics is by no means entirely clear. Superinfection with gram-negative following penicillin therapy has been observed by us within a few days to a week. On the other hand, penicillin prophylaxis of rheumatic children over a long period of time has not resulted in such changes in our series of cases. The prophylactic and therapeutic value of a broad-spectrum antibiotic, such as terramycin, is clearly evident in cystic fibrosis of the pancreas from the observations of Dr. Shwachman. Such long range prophylaxis appears to be similar to prevention of rheumatic fever by means of penicillin.

Dr. Lepper: It stands to reason the higher the dose and the more prolonged the dose, the more complete eradication, the more chance for superinfection. More important is the environment under which the treatment is being given than the dose and duration. The environment in the hospital is where we get most of our superinfections. With staphylococci, for instance, we did a study at our hospital over the last year and a half and found that 72% of our personnel carry penicillin- and aureomycin-resistant staphylococci. Patients come in with about 50% resistant forms in their nose and/or throat; if they get no therapy they jump up to about 65%. By the time they go out, if they get penicillin or aureomycin they jump to 80 or 90%. You probably will not get that same increase in the home.

Dr. Stanley L. Harrison, St. Louis: Dr. Lepper, you brought up the question of the use of antibiotics frequently, by pressure from the family. I have noticed the same thing—children who are ill frequently during the winter because of repeated injections of antibiotics that are not adequate. I would like to have you comment on that.

Chairman Neter: I am sure that everyone will concur with what you have said. The promiscuous use of antibiotics is to be deplored. The pediatrician may find himself in a difficult situation; if he does not use an appropriate antibiotic and the upper respiratory tract infection becomes complicated by otitis media, he will feel as unhappy as having used such an agent without indication and without benefit and particularly if this treatment is followed by undesirable side effects. The possibility exists that treatment of a given infection in the earliest stages by an effective antibiotic may interfere with antibody formation and subsequent development of immunity. In addition, it is painfully clear to everyone that inadequate antibiotic therapy in such instances may delay the clinical and laboratory diagnosis and thus optimal therapy. One may add that even in this era of antibiotic therapy and fully conscious of the extraordinary advances made in the field of infectious diseases by the judicious use of these potent agents, aspirin, in proper dosage, still has a place in the armamentarium of the pediatrician.

Question: What is the feeling regarding the use of local antibiotics—eye drops, nose drops, ear drops?

Dr. Lepper: In general, we don't feel that local use is too good; most local use is too transient. In the hands of the specialists, apparently you can get fair results and if you do have superficial eye infections you get fairly good results with local administration. In most situations more can be accomplished by parenteral therapy. It is certainly an unanswered problem. We feel that the problem of superinfection may be great.

Dr. Horst Agerty, Philadelphia: I have seen one case of thrombocytopenic purpura that seemed to follow the administration of penicillin. Do you have any experience with this?

Dr. Lepper: I haven't seen any cases like that in which we felt it was due to that drug. There almost always is an infection present and that makes cause and effect rather difficult to decide.

Symposium

SURGICAL PROBLEMS IN CHILDHOOD

HERBERT E. COE, M.D., Seattle, *Chairman;* ALEXANDER H. BILL, JR., M.D., Seattle; ORVAR SWENSON, M.D., Boston; C. EVERETT KOOP, M.D., Sc.D., Philadelphia; HENRY W. HUDSON, JR., M.D., Boston; OSWALD S. WYATT, M.D., Minneapolis

INTRODUCTION

HERBERT E. COE, M.D.

At the Toronto meeting of the American Academy of Pediatrics it was suggested that the Surgical Section be responsible for a portion of the program at the next annual meeting, the presentations to be in the form of a symposium. Articles relating to surgical conditions in infants and children frequently appear in current medical literature presenting opinions which are often divergent, or even conflicting, and members of the Academy have often commented on this apparent confusion. It seemed timely, therefore, to select several of the more common of these conditions and assign each to a member of the Surgical Section for a discussion which might reasonably be expected to represent one of the views more generally accepted by surgeons primarily interested in children. Complete unanimity is of course not to be expected nor desired, as an honest difference of opinion promotes healthy discussion and progress.

Several of the comments on the presentations indicated that panel discussions on some of the subjects would be most interesting and might well be included in future programs.

The close attention and favorable reaction of the audience was most gratifying, and it was regrettable that Dr. Potts who planned and coordinated the Symposium was prevented by illness from acting as chairman. Illness also prevented Dr. Wilkinson from presenting his discussion on "Bronchiectasis" but fortunately his time could be made available for the Honorary Life President of the Surgical Section, Dr. William E. Ladd, whose excellent address will be long remembered by all who heard it.

PECTUS EXCAVATUM (FUNNEL CHEST)— A MEDICAL OR SURGICAL PROBLEM?

ALEXANDER H. BILL, JR., M.D.

(To be published as an original article)

INGUINAL HERNIA IN INFANTS AND CHILDREN

ORVAR SWENSON, M.D.

This study is based on 506 infants and children on whom herniorrhaphies were performed. Two hundred seventy-one of the patients were infants under 2 years of age, and practically all 64 patients who were treated for incarceration were in this lower age group.

Patients who presented themselves with left inguinal hernia were carefully examined on the right side. Of the 153 patients with left inguinal hernia a sliding sensation on palpation of the cord on the right side prompted bilateral exploration on 73, and 65 of these patients were found to have right inguinal hernial sacs as well as the obvious left hernia. Out of the 80 with left-sided hernia in whom the right side was not explored 12 have so far returned for repair of a right hernia. These statistics emphasize the importance of considering bilateral repair in patients who present themselves initially with a left inguinal hernia. On the other hand, patients who present themselves with a right inguinal hernia rarely have a left. Out of 245 patients who presented themselves with right

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inguinal hernias it was decided to do bilateral exploration on 17 after careful examination of the left side. In 15 of these a left inguinal hernia was found. Out of the 228 patients only 4 subsequently presented themselves with a left inguinal hernia. This figure is probably inaccurate because some patients may have had a second herniorrhaphy elsewhere. It appears that patients with initial left inguinal hernia have about a 50% chance of developing one on the right side. On the other hand, those patients who present themselves with a right inguinal hernia only have a slight chance of subsequently developing one on the left side.

There have been relatively few postoperative complications in this group of 506 patients. There were no deep wound infections in any of the patients. In 4 incisions superficial redness occurred, and one or more subcuticular silk sutures extruded from the wound. In view of this we believe subcuticular closure with collodion painted on the wound and no gauze dressing is amply justified. There was one recurrence in this series. The single postoperative death occurred in an infant with incarceration which could not be manually reduced and required an emergency operation.

UNDESCENDED TESTICLE: DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

C. Everett Koop, M.D., Sc.D. (Med.), F.A.A.P.

The phenomenon of an empty scrotum may indicate undescended, retracted or absent testicles. Traditional misconceptions concerning the empty scrotum include the belief that cryptorchidism is far more common than it is, that it is frequently corrected spontaneously, that the testicles finish their embryologic descent at puberty, and that injected hormones are beneficial in hastening the descent of the testicle or in making certain of that process at puberty.

Careful examination of the patient's inguinal area and the attempt to milk the testicle into the scrotum will indicate whether one or both testes are present, whether a testicle high in the inguinal canal can or cannot be pushed into the lower scrotum, and whether the condition is unilateral or bilateral. Any combination is possible—testes may be unilaterally or bilaterally not palpable, retracted, or embryologically undescended. Any 2 conditions may co-exist.

If a testicle can be brought into normal anatomic position by manipulation, that gonad is physiologically retracted and the patient needs no therapy.

If the testicle can be palpated but cannot be brought into the normal position by manipulation, a congenital defect is present which cannot be corrected by nonsurgical means, except in the very rare case in which the undescended testicles are part of an endocrine arrangement with other obvious stigmata.

When a testicle cannot be palpated in the scrotum or canal, it means that the testis is either atrophic, nonexistent, retroperitoneal, or impossible to feel because of over-lying inguinal fat.

Only the undescended or nonpalpable testis is a therapeutic problem. If either of these is unilateral, the problem of sterility is not of primary concern. The indications for operation in unilateral cryptorchidism are cosmetic, physiologic, or associated with the indirect inguinal hernia which is almost always present with an undescended testicle.

When the problem is bilateral, the avoidance of sterility is of primary concern. We suggest surgical treatment of unilateral or bilateral undescended or non-palpable testes

Success with operation almost always depends on the length of blood supply. Since the blood supply is usually more elastic and redundant in young children, there is an age of election for orchidopexy. Certainly, the operation should be accomplished in the preschool years and our experience would indicate the greatest number of successful procedures can be expected in the very young.

A definitive opinion concerning the future position of the testicle can usually be made in the first postoperative months.

BLEEDING FROM THE BOWEL

Henry W. Hudson, Jr., M.D.

Bleeding from the bowel, large in amount and recognizable as blood, is not only alarming but also is an indication of a surgical emergency. A sporadic incident, with blood in small amount, justifies an expectant attitude and the educated guess that the explanation is minor trauma. Reference

is made to some of the general disturbances in which bleeding may be a sign but this discussion is limited to conditions which have surgical implications. Foreign bodies whether ingested or introduced through the anus, local trauma, and blood swallowing are mentioned. Diaphragmatic hernia, Meckel's diverticulum, duplication of segments of the intestinal tract, atypical intussusception, polyp or polyps, are discussed and illustrative cases cited. Other lesions included are hemangioma involving the bowel wall, carcinoid lesions, leiomyoma, carcinoma and portal hypertension. Reference is made to the disturbingly large group in which no diagnosis is established even after investigation, including exploratory laparotomy, has been carried out. In this group, trauma from unrecognized foreign bodies is a suggested explanation.

When a patient with melena or suspected melena presents, when no physical abnormality is discovered, and when hematologic study is negative the diagnostic approach may be as follows:

1. Chemical or microscopic confirmation that what appears to be blood is blood
2. Digital and endoscopic examination
3. X-ray examination by means of barium enema
4. Proctosigmoidoscopic examination after suitable preparation and, usually, under anesthesia with preparation to follow by
5. Abdominal exploration under full anesthesia with adequate exposure and with an orderly inspection and palpation of the intestinal tract from the rectum to the cardia.

INTUSSUSCEPTION IN INFANCY

O. S. WYATT, M.D.

After the first few weeks of life acute intussusception is the most frequent type of intestinal obstruction encountered during infancy. It behooves every physician to substantiate or rule out this entity once suspicion is aroused.

Any infant that has passed blood and mucus by bowel must be seen within the hour, and for one of us to give the mother an assuring answer, or prescribe over the telephone is pure neglect, and abuse of our obligations and responsibilities.

If the onset is violent it is probably a tight intussusception and the baby will be in shock. Fully 50% of babies with intussusception do not present shock. Vomiting is not an early symptom in acute intussusception. Assumption of the knee-chest position is almost pathognomonic for enterocolic intussusception. "Red-current jelly" stool rarely occurs under 6 hours.

Administration of chloral hydrate helps to carry out satisfactory abdominal palpation. The triad of (1) intermittent abdominal pain, (2) blood and mucus by bowel, (3) palpable abdominal tumor makes the diagnosis of intussusception certain.

Many intussusceptions can be reduced by barium enema, when seen in the 1st 4 to 12 hours. Given a late intussusception or a very shocky baby do not attempt reduction by a barium enema, this is definitely a surgical problem.

Now I presume it is heresy for a pediatric surgeon to talk about the nonsurgical management of acute intussusception. On the contrary, I have become convinced that about 50% of early intussusceptions can be treated safely in this manner. As a result the management of early acute intussusception becomes as much a problem for the pediatrist and roentgenologist as for the surgeon.

Certain pitfalls must be kept in mind when reducing an intussusception with a barium enema. They are: 1. incomplete reduction; 2. injury to appendix and its blood supply; 3. over-looking an enteric intussusception; 4. rupture of the gut.

I do not agree that it is quite as easy or safe as some quarters would like us to believe, but I do believe that with acute observation and repeated examinations you can keep your baby out of trouble.

Again may I emphasize that a barium enema is not justified as a therapeutic agent, if the onset of the intussusception was violent and the baby presents severe shock. Neither do I feel that barium should be used if you are dealing with an intussusception that is over 12 hours in duration. Even after blood has been passed I can see no objection to using barium as a diagnostic measure, but if the intussusception cannot easily and readily be reduced, surgery should be resorted to at once.

A thorough gastric lavage must be done, and an indwelling gastric catheter in place before going to surgery. Shock if present must be treated, an intravenous catheter in place, and functioning properly. Have glucose flowing, plasma connected, and blood available.

At surgery inspect ileocecal junction to make sure reduction is complete. Search for a Meckel's and if involved in intussusception remove. If the appendix has been caught in the intussusception remove. Perhaps more frequently than we realize, appendicial pathology may initiate an intussusception.

In closing may I again emphasize careful history, early examination and diagnosis, followed by immediate reduction, and I am confident that the mortality of intussusception in infants will be markedly reduced throughout the nation.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

DEAR DR. HARPER:

I appreciate very much your invitation to bring to the readers of PEDIATRICS information about summer assignments in the Public Health Service, the qualifications required and the results that may be anticipated from a few months' experience with our Service.

For more than four years, now, the Public Health Service has made available summer employment to a limited number of students in medical, engineering, and basic science professions. The practice has proved beneficial to the Service in providing assistance to selected public health clinical and research projects. It also has offered actual working experience in a supervised environment for students in the medical and allied scientific fields. Many students and a number of deans have expressed appreciation of the opportunities which summer employment has contributed to the professional training and development of the students.

Our reason for initiating the summer program has been twofold. We need the temporary assistance of competent students in many of our operating and research programs and we want more students to become acquainted with the reasons for the conduct of public health activities.

Students selected for these assignments receive civil service appointments which begin at the close of the academic year and terminate early in September. The salary is $284 a month.

These summer assignments cover a wide area of Public Health Service activity. They range from laboratory research projects at the National Institutes of Health to investigations of communicable disease problems at the Communicable Disease Center; from clinical assistant posts in venereal disease clinics to assistant-ships in our psychiatric hospital; from studies of industrial plant hazards to epidemiological investigations of psittacosis. We are convinced that summer experience of this variety offers to students in the medical and allied sciences a breadth of experience not often available in the pregraduate years.

At the National Institutes of Health last summer, for example, one medical student acted as a research assistant in a psychiatric study. Another student observed and recorded clinical observations made of infants' psychological and physiological reactions to change in nursing schedules, weaning, and other variations in environment. Still other medical students assigned to the National Institutes of Health undertook specific research assignments in the fields of heart, arthritic and metabolic diseases. These assignments provided the participating students with knowledge of a variety of laboratory procedures, both routine and experimental, and gave them some insight into the problems incident to medical research.

Assignments of second and third year medical students at the Communicable Disease Center in Atlanta, which is concerned with public health problems presented by various infectious diseases, offer considerable experience in disease investigations. One of last year's students who was assigned to a poliomyelitis survey worked with an epidemiologist who assisted several State health officers in the investigation of outbreaks of polio. During the course of the assignment, the student had an opportunity to perform physical examinations, to obtain and review case histories, to examine x-rays and collect specimens. Similar experience was afforded other students assigned to investigations in psittacosis, encephalitis and dysentery.

Third year medical students who were employed for clinical assignments in the venereal disease program served in clinics under the direction of State and local health officers. They performed physical examinations, analyzed the results of laboratory tests and made diagnoses of venereal and other diseases. They carried on their work under the direct supervision of the physician in charge of the clinic. They also took part in field investigations designed to improve case finding activities and assisted with other venereal disease control projects.

Assignments to research activities in our psychiatric hospitals involved taking measurements of respiratory minute volume, pulse rate and body temperature, taking electrocardiograms and electroencephalograms, assisting in surgical operations on laboratory animals, recording the outcome, evaluating the resulting material and combining this analysis with other information relating to drug addiction both in animal and in human subjects.

Veterinary students last year were assigned to epidemiological studies in psittacosis, encephalitis and anthrax and field investigations of rabies in wild life. Engineering students did research and investigation work concerned with sewage and waste disposal, water pollution control, industrial plant hazards, hookworm control and public health inspection techniques in housing sanitation. Graduate students in biology, entomology, bacteriology and mycology worked in a number of disease control, water analysis and insect survey projects.

The Public Health Service has already notified the deans of a selected list of medical schools, colleges and universities concerning the assignment of students to positions within the Public Health Service during the coming summer. Since the Public Health Service cannot pay travel expenses of students selected for summer employment, announcements are, in general, addressed to schools located near our installations. However, inquiries will be welcomed from students who are interested in receiving detailed information about the program.

W. PALMER DEARING, M.D.
Deputy Surgeon General
Washington, D.C.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE MAGNUSON COMMISSION RECOMMENDATIONS FOR CHILD HEALTH

THE Report of the President's Commission on the Health Needs of the Nation has already received a great deal of attention in both medical journals and the lay press. Its recommendations are far-reaching: federal aid to medical education "to supplement, not replace, state appropriations and private gifts" under conditions in which "the preservation of the administrative autonomy of the schools must be secured"; "an adequate system of hospitals and related health facilities to serve all of our people in both urban and rural areas"; federal subsidies for prepayment medical care plans and the expansion of group practice; and the creation of a cabinet-rank Department of Health and Security. The report reviews existing health conditions and outlines general and specific proposals aimed at "the building up of our health resources in terms of training more health personnel and providing more physical facilities."

It is not our purpose to review the report as a whole, but more particularly to call attention to those parts which deal especially with children. At the same time it should be recognized that almost every section of the first volume published under the title of "Building America's Health" has implications for the health of children. Here are some of the things the report[1] says:

"Today there are more children than at any other time in our history, more than 47 million under 18 years of age. During the decade 1940 to 1950, the number of children under five years of age increased 53 percent. Each year has seen a great improvement in child health. Nevertheless, there remain many deficiencies in health services to the children of this Nation.

"Enormous gains have been made in the prevention and cure of disease among children. Child-bearing has never been safer. Many diseases which were once prevalent in the childhood years have now largely disappeared. In fact, the whole base of medical care for children is now changing from the treatment of disease to the promotion of health. We are emerging from an era of activity where physicians, nurses and social workers were rushing about taking care of sick children, to an era when knowledge and time are becoming available to help the well stay well. In short, health care is shifting from the defensive to the offensive.

"From our present vantage point we see many needed steps along the road to the objective of good health services for all mothers and children.

"First is the need for more well-trained physicians, dentists, nurses, social workers, and others who in their professional capacities assume responsibility for the health and

[1] Building America's Health, a Report to the President by the President's Commission on the Health Needs of the Nation. Findings and recommendations, vol. 1, Washington 25, D.C., U. S. Government Printing Office. Quoted with the approval of the Commission.

welfare of children. All of these disciplines require still greater emphasis upon the problems peculiar to the emotional and physical growth of children.

"Second is the need to overcome the barriers to good medical care which result from geographic and from economic causes. In those sections of the country where physicians, hospitals, and other health resources are deficient, and where per capita income is low, the quantity and quality of health services for children and mothers are proportionately low. Three measures can do much to remedy these inequities: (1) extension of local public health services, (2) provision for special diagnostic and consultation service in pediatrics and obstetrics for rural communities, and (3) regional planning. The first is part of the move to establish local health units throughout the Nation. No matter what other services are included in a local health unit, maternal and child health services invariably receive prominent attention. Regional planning, given special emphasis by the American Academy of Pediatrics as a result of its nation-wide survey of child health services, is one means of creating a direct channel between the urban center and the rural services. It brings to the remote areas the benefits of the latest research, new procedures and high quality services of the medical center.

"Third is the need for more research in the field of child life, to improve existing techniques and to raise the standards higher. Particular attention should be given to two factors which still stand as leading causes of death and disability—premature birth and accident.

"One long overdue measure for child health is concentrated action directed at the problem of the distressingly large number of children who are emotionally disturbed, mentally deficient, mentally ill, or suffering from epilepsy. In no other area of child life has so little progress been made. The problem does not involve the child alone, but rather the child as a member of the family unit. The family must be accepted as the irreducible unit for health service. Unfortunately one out of nine children lives in a home broken because of divorce, separation, or premature death of parents. Such disrupted families often give rise to emotional abnormalities not only in childhood but also in later life.

"Vast sums of public money are being spent each year on school health examinations. How often have children and parents been needlessly alarmed because of hasty misinterpretation of some innocuous finding by a school physician? Less time should be spent on perfunctory annual examinations of school children as they are too often performed today. More time should be devoted to careful health screening and follow-up, including medical consultation with parents as well as school teachers, and in the utilization and development of community resources for diagnosis and treatment. School health programs would then become far more productive of good results.

"The goals of child health cannot be met without the co-operative effort of official and voluntary agencies of the community. To attain these goals will require more money for more services. But the answer lies also in better use of existing resources. Continuing effort is needed to evaluate the work of the agencies serving children, and to provide them with guides to improve their programs.

"We, therefore recommend that:

"1. Education of general physicians, dentists, nurses, social workers, teachers, and others on the health team include a better understanding of the development of the physical and emotional life of the child and mother. Our general public educational system should emphasize the health aspects of childhood and motherhood.

"2. Local public health services be extended to cover the entire country, including isolated rural sections.

"3. Provision be made for an adequate number of hospital beds and nursing care for children of all ages, including special provision for the premature infant.

"4. Provision be made for diagnostic and consultative services in pediatrics and obstetrics for rural areas and wherever else needed.

"5. Program for the care and training of children with mental deficiency and epilepsy be strengthened.

"6. Research be undertaken into the causes and prevention of childhood accidents; into the effectiveness of health programs for children; into the causes and prevention of fetal mortality, premature birth, neonatal mortality, mental deficiency and epilepsy; and into child development, both emotional and physical."

The importance of dental disease and defects is emphasized as follows:

"An array of shocking evidence establishes the high priority which dental care deserves among the health needs of the American people. Sufficient dental care either is not available or is not utilized by the American people to a degree even approaching an adequate level.

"A survey of school children in one city disclosed that 70 percent of those 12 years of age had one or more permanent teeth that needed to be filled and that by age 15 the proportion was 85 percent. A study by the American Dental Association in 1940 revealed that among young persons 15-24 years of age coming from families with an income of $3,000 or more, one-sixth required bridges or dentures. Among older people the prevalence of dental disease and defects is well-nigh universal. This includes a vast amount of disease of the gums and other peridental disease as well as defects of the teeth themselves.

"Against this evidence of need, it should be noted that less than 40 percent of the American people receive any dental care during the course of a year. These data clearly indicate the large gap between needed dental care and the amount actually provided.

"In large part this gap reflects our past widespread acceptance of dental decay and ultimate loss of teeth as inevitable. Until recent times, as a matter of fact, not much was known about the prevention of dental disease and there was little application of this knowledge. Continuation of a resigned attitude toward dental disease, however, is not consistent with our present knowledge.

"We now have procedures which, if fully applied, would prevent a great amount of dental disease and correct a large proportion of existing defects.

"Fluoridation of communal water supplies is now in effect for 475 communities with a combined population of nearly 11 million. An additional 353 communities with 17 million persons have approved this means of preventing dental decay. Excessive indulgence in refined carbohydrates, as well as deficiency of fluoride in drinking water, may be a significant factor in the poor dental health in this country.

"However, even though a wider application of preventive measures will ultimately reduce the need for dental care among our people, the need for dental care will continue at a high rate for many years to come.

"Effective use of auxiliary dental personnel would significantly increase the amount of service which dentists could provide. According to a study by the American Dental Association, dentists with one employee were able to see 37 percent more patients than did dentists with no employees, while dentists with two employees could see 69 percent

more patients. Yet, only three-fifths of all dentists employ even one full-time dental assistant or dental hygienist.

"We, therefore, recommend that:

"1. Dental care be considered an essential component of comprehensive health service, to be made available for children immediately, and for the entire population as rapidly as possible.

"2. All communities bring the fluoride content of their communal water supplies up to an optimum level for the prevention of dental caries, and that individual preventive dental procedures likewise be promoted.

"3. More efficient methods of dental practice, including the more general use of dental assistants and dental hygienists, be undertaken.

"4. Increased research into dental disease be supported."

Attention is also given to childhood accidents. The report states:

"Accidents among children present a growing problem to parents, pediatricians, and others responsible for the health and welfare of children. Three fatal accidents occur among children under 15 years of age every two hours throughout the year. The most frequent cause is motor vehicle accidents, followed by drowning and burns. In the home poisons taken accidentally cause many deaths. Accidents constitute the greatest single threat to children's lives and physical health. Local health departments, safety councils, school officials, together with the general physician, need to cooperate in attacking this scourge of childhood."

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

INTERNATIONAL NON-PROPRIETARY NAMES FOR DRUGS

STANDARDIZATION of terminology for drugs and scientific substances appears to be a highly desirable goal. Exchange of information through publication and individual communication would be far less subject to misinterpretation if nomenclature were precise and unchanged. Furthermore, increase in world travel makes it more necessary than ever that patients, physicians, and pharmacists be able severally to request and comply with requests for drugs without worry about differences in names. International health co-operation and regional health program would obviously benefit from simplification of terminology.

The situation has recently been reviewed by P. Blanc, Secretary of the World Health Organization Expert Committee on the International Pharmacopoeia, before the International Pharmaceutical Federation. His paper has been summarized in the Chronicle of the World Health Organization, for November 1952, volume 6, page 322, from which the following extracts are taken:

"At first sight it might seem that, for the numerous drugs which are chemical compounds, the chemical names could be used; but the latter are often so complicated that manufacturers and sales agents spontaneously adopt simpler and shorter names. Obviously 'riboflavine' sounds better and is more easily remembered than 6:7-dimethyl-9-(D-1′-ribityl)*izo*-alloxazine. But, unfortunately, the same substance is known elsewhere by the name of 'lactoflavine' or 'vitamin B_2'. Another example may be cited, namely that of the methadone hydrochloride of the *Pharmacopoea Internationalis* (6-dimethylamino-4,4-diphenyl-3-heptanone), which is known in different countries under the following names: amidone, miadone, diadone, diaminon, mephenon, symoron, etc.

"The first commission for international pharmaceutical nomenclature was established in 1915 under the auspices of the International Pharmaceutical Federation. A second commission was appointed in 1922; and, as early as 1924, a first list of names was submitted to national pharmacopoeia commissions. Some of them adopted this list, arranging to have placed after each name initials identifying it as belonging to the international nomenclature.

"The Brussels Agreement of 1929 suggested to the pharmacopoeia authorities of the signatory countries international names for a series of so-called potent drugs, for which specific standards were indicated. Furthermore, one of the articles in the Agreement assigned to the future permanent international pharmacopoeia secretariat (which was to be set up under the auspices of the League of Nations) the duty of formulating proposals which might lead to a uniform nomenclature in pharmacopoeias. The said secretariat has since come under the aegis of WHO.

"The Expert Committee on the Unification of Pharmacopoeias of the WHO Interim Commission was established in 1947. At its second meeting, in June 1948, this committee expressed the wish to seek the co-operation of the International Union for the

Protection of Industrial Property, with the aim of introducing non-proprietary names for drugs.

"In October 1948, a member of the expert committee submitted a note requesting WHO to standardize non-proprietary names and to create, introduce, and have adopted international non-proprietary names for new pharmaceutical chemical compounds, whether included or not in the International Pharmacopoeia. He suggested that these names be in Latin and that they, as well as their translations into the various languages, enjoy international protection and not become the property of business concerns or of individuals.

"In January 1949, the Expert Committee on Habit-Forming Drugs recommended, in turn, 'that a mechanism should be established whereby every habit-forming drug subject to international control, can be given a single name to be used for all international purposes.'

"The Expert Committee on the Unification of Pharmacopoeias consequently set to work to fulfil the wishes expressed in various quarters and, in 1950, a series of guiding principles for the selection of international non-proprietary names was submitted to the Third World Health Assembly. These principles are as follows:

(1) Names should, preferably, be free from any anatomical, physiological, pathological, or therapeutic suggestion.

(2) An attempt should first be made to form a name by the combination of syllables from the scientific chemical name, in such a way as to indicate the significant grouping of the compound.

(3) Names should, in general, not exceed four syllables.

(4) Names should be distinctive in sound and spelling, and should not be liable to confusion with names already in use.

(5) Names which are difficult to pronounce or to remember should be avoided.

(6) The addition of a terminal capital letter or number should be avoided.

(7) Names already used in the national pharmacopoeias or officially adopted in any country, or which are included in *New and Nonofficial Remedies,* should receive preferential consideration.

(8) The following terminations should be used:

Latin	English	
-inum	-ine	for alkaloids and organic bases
-inum	-in	for glycerides and neutral principles
-osidum	-oside	for glycosides
-olum	-ol	for alcohols and phenols (-OH group)
-alum	-al	for aldehydes
-onum	-one	for ketones and other substances containing the CO group
-enum	-ene	for unsaturated hydrocarbons
-anum	-ane	for saturated hydrocarbons

"The first principle arises both from the desire not to give the patient the idea of some definite disease and from the fact that the therapeutic indications for certain new products have been found in practice to be different from those originally attributed to them.

"Principles 2 and 3 are generally accepted and applied. As regards principles 4 and 5, they refer to those cases, no doubt frequent, in which a given non-proprietary name must be amended in a country so as to avoid confusion with common names or with registered trade-marks.

"Principle 6 is generally accepted by national pharmacopoeia commissions, and it is considered preferable, for example, to adopt 'ascorbic acid' rather than 'vitamin C'.

"Principle 7 encourages the adoption, by preference, of names already employed in the country where the new product has been discovered and put on the market for the first time. This important principle complies with numerous requests, including that of the World Medical Association. The Expert Committee on the International Pharmacopoeia has also declared that any name suggested by the person making a discovery, if it is not contradictory to these principles, should be given favourable consideration.

"Principle 8 (the endings to be used) must be applied on a fairly wide basis so as to cover the majority of cases. It is possible that it may be subsequently amended and extended. International non-proprietary names will always be established in Latin, with French and English translations.

"It is recommended, furthermore, that all products which have received an international non-proprietary name and which are sold under a trade-mark should also bear the international non-proprietary name on the label.

"The above principles were communicated to WHO Member States in April 1950. Thirty-two Member States have declared themselves to be in general agreement with the principles approved by the World Health Assembly. Exchanges of views have taken place with several national pharmacopoeia commissions and with various interested national or international organizations.

"A Subcommittee on Non-Proprietary Names has been attached to the Expert Committee on the International Pharmacopoeia. Since its creation, this subcommittee has selected or approved several hundred international non-proprietary names. Lists of non-proprietary names for the drugs to be included in Volume II of the *Pharmacopoea Internationalis* and for certain other drugs have been published in *World Health Org. techn. Rep. Ser.* 1951, 35, **28**: 48, 30. The names are chosen as follows: National Pharmacopoeia authorities and other competent bodies are asked to invite manufacturers and research laboratories to inform them of new pharmaceutical products which might later be incorporated into the International Pharmacopoeia and for which it would be necessary to adopt international non-proprietary names. They are also requested to inform WHO of these products. When necessary, to save time, manufacturers, research laboratories, and universities may report these products directly to WHO. Between the sessions of the Expert Committee on the International Pharmacopoeia, suggestions presented by a member or by one of the above-mentioned authorities are communicated in writing to the chairman of the subcommittee, who submits a proposed name to the other members of the subcommittee. If they do not accept this proposal, they inform the chairman to this effect. The chairman is empowered to select the final name after one or two exchanges of views. Whenever possible, the subcommittee collaborates closely with the pharmacopoeia authorities.

"All this represents a very difficult task. It is necessary to search out the names which are registered or in use in the various countries so that the proposed names will not duplicate those of already existing trade-marks. Furthermore, measures must be taken with a view to 'preventing the use of names selected for unauthorized purposes' and to prevent individuals or commercial enterprises from taking over these names for their own purposes.

"Two methods have been suggested to ensure protection for international non-proprietary names. The International Union for the Protection of Industrial Property

might study the possibility of including provisions to this effect in the International Convention for the Protection of Industrial Property. In addition, the Expert Committee on the International Pharmacopoeia and WHO could suggest to the World Health Assembly the adoption of international regulations by virtue of which Member States would pledge themselves to give effective protection to the international non-proprietary names."

Precision of meaning and uniformity of expression are directly related to ease of communication. With all the other intricacies of medical science this principle becomes even more fundamental. Interest in standardization of nomenclature is therefore incumbent on every physician. Through effective cooperation of individuals and organizations, such standardization is achievable.

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

SOME POTENTIAL HAZARDS OF THE USE OF ROENTGEN RAYS IN PEDIATRICS

By ROBERT W. MILLER, M.D.
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THE PROBLEM AND THE PURPOSE

Progress in pediatrics today is often attained through the development of technics that make use of fluoroscopy. This, for example, has been the case in the detection of congenital anomalies of the cardiovascular system. Fluoroscopy is used in the diagnosis of cystic fibrosis of the pancreas to place the catheter properly for the aspiration of pancreatic enzymes. As physicians make more widespread use of such technics, realization that the detrimental aspects of ionizing radiation have been underestimated may become more apparent. This paper attempts to bring to the clinician's attention the work that has been done in radiobiology, what lies ahead, and how this information relates to pediatrics.

MECHANISM OF RADIATION EFFECTS

X-rays are composed of packets of energy called quanta which will cause the orbital electrons of atoms to be displaced as the radiation passes in their vicinities. When a molecule of a cell is thus ionized, it must become rearranged in stable form as quickly as possible. This may be accomplished by the formation of new compounds within the cell. The result of this may be an altered physiology.[1,2] If the change is sufficiently severe, the morphology of the cell will be altered so that microscopic or gross aberration can be demonstrated. It must be realized that with low doses functional changes in a single cell can occur that would not be measurable by known laboratory methods. Certain special substances or large molecular entities which are strategically located within the cell and present in limited amounts, such as the genes, once affected may not be restored.[2] Consequently the function which they controlled may henceforth be abnormal if the cell does not die as a result of the injury. Functions which involve molecules which are not in this "special agent" category will recover, it is believed, following the acute phase of the injury. Of course, as is now popularly known, when germinal mutations occur, several normal generations may pass before the abnormality becomes clinically manifest.[3] Grossly unappreciated is the chance that somatic cell changes (possibly mutations) may contribute to disease processes many years after the exposure to x-rays.[4,5]

Because of the small size of the infant's body, a much greater percentage of him is exposed for routine fluoroscopy than occurs when an adult is subjected to the same pro-

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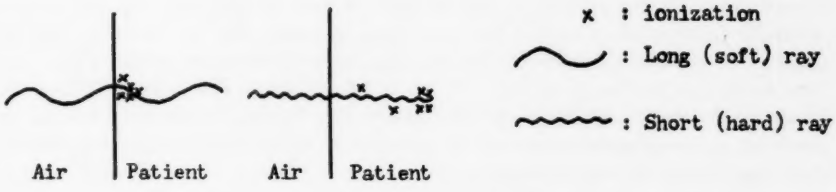
cedure. The dose received by the patient will be proportionate to the amperage and voltage of the machine used, the filtration, duration of the exposure, distance between the roentgen tube and the patient, and the volume of the infant's body.[6,7]

To understand better the material that is to follow, it is best to recall at this point that a "hard" x-ray is one with a high energy and a short wave length. "Soft" x-rays have a long wave length and a low energy. Roentgen values mentioned below refer to the measurement in air at the point of entry into the patient's skin.

The pattern of response of tissues is the same regardless of the wave length of the radiation. However, the location and extent of the injury does vary with the wave length. The longer rays produce their paths of densest ionization, and therefore greatest injury, closer to the exposed surface than rays of greater energy will do.[2] Diagrammatically this physical event would look like this:



Thus it can be seen why lower energy x-rays will produce erythema of the skin with less dosage than in the case of high energy rays.

Skin erythema occurs when a patient receives a dose of radiation that exceeds his tolerance for this manifestation. There exists in this instance a threshold for the production of the radiation effect. If 400 r is the threshold for an individual for a single exposure, no cutaneous reddening will occur until he has received at least this dose. It is believed, on the other hand, that genetic mutations occur in a direct proportion to the x-ray dose administered, no matter how small that dose may be. It has been experimentally shown that the fruit fly, *Drosophila,* irradiated with 25 r develops one-tenth the increase in mutation rate that 250 r will create.[3] It is thought that this is a nonthreshold response, and because of this no tolerance range exists.

If a dose of x-irradiation is given in divided fashion with a rest period between each sitting (fractionation of dose), there will be incomplete summation of acute effects. That is, there will be less damage done than if the entire dose were given at a single exposure. This is not true, however, for nonthreshold events. Here the effects produced can be considered to be additive. Late biologic effects of x-ray may be in this category.

Dougherty and White's work[8] exemplifies the concept that tissue may be damaged indirectly. When 10 r of whole body irradiation was administered to mice, a lymphopenia was observed. Adrenalectomy abolished this response. The conclusion was that the lymphopenia produced at this dose level was indirectly brought about through a disturbance of the pituitary-adrenal cortical balance and not through a direct effect on the lymphocyte.

Within the same species the sensitivity to x-irradiation varies greatly. Death or radiation sickness will take place in some at a lower dose level than in others. Rapidly dividing cells and undifferentiated cells are generally more susceptible than others. This is exemplified by the fact that embryos are especially sensitive to x-rays. There has been

some work done to illustrate that young animals are more apt to be affected than adults by exposure to radiation.[9, 10] It has also been shown that in some instances the state of health of the animal will change its susceptibility. Hyperthyroid mice die sooner following irradiation and have a greater total mortality than do normal animals.[11]

Certain areas or organ systems of the body exhibit a greater sensitivity to radiation injury. Exposure of the abdomen has been observed to cause radiation sickness at a lower dose level than would happen if the same dose were applied to another part of the body comparable in volume.[12,13] The tissues most sensitive to acute roentgen effects are growing bone, the hemopoietic centers, the gonads and the gastrointestinal tract.

Therapeutic and Diagnostic Roentgen Dosages Involved in Pediatrics

Fluoroscopic dosages have been measured by physicists and radiobiologists[6, 7, 14–17] to be between 6 and 40 r, usually 10 to 20 r/minute in air at the point of entry into the patient's body. If the duration of the examination is 2 to 5 minutes, the dose would ordinarily be 20 to 100 r. Certain patients, such as the infant with malnutrition, recurrent diarrhea, or repeated pulmonary infections, may suffer an exposure within a few days time which easily adds up to 150 r if the full lot of chest fluoroscopy, G. I. series, barium enema studies, and duodenal intubation is run. The studies mentioned would include the upper abdomen commonly, so this region, a particularly sensitive one, would get a large share of the total exposure.

Hills and Stanford[18] have pointed out that in the "routine investigations of the heart" (including fluoroscopy, angiocardiography and catheterization) about 140 r are delivered to the patient's chest. In their evaluation they include only one fluoroscopic examination whereas several are usually done before the studies are complete. The target-to-skin distance described by these investigators is greater than that commonly used, and this too would reduce their estimate of total dosage.

On the other hand, the exposure involved in securing an x-ray film study is usually about 1.2 r/film.[14] A chest film requires only 0.05 r. If fluoroscopy of the chest is performed instead, and 15 r is the dose administered for the procedure, the patient is exposed to 300 times the dosage he would receive for a film study.

In securing a gastrointestinal series the total exposure includes both that provided by the fluoroscopy and by the film studies. An intravenous pyelogram requires 1.2 r/film, so that approximately 8 r is necessary for the series of plates. Dental films average about 5 r each, with an individual exposure ranging as high as 15 r.[6] The reason for this high dose is the short tube-to-skin distance.

The recommended therapeutic x-ray doses[19, 20] are generally greater than even the accumulated fluoroscopic ones. Shrinkage of the thymus is usually accomplished by a single exposure of 75 r, but sometimes repeated treatments totalling 350 r are given.[19] Similar doses are suggested for the treatment of the cough of atypical pneumonia. The fractionated roentgen therapy of acne may reach very high levels, especially if the patient changes doctors frequently or if the physicians are untrained in radiation therapy.

The figures for fluoroscopy may not seem impressive when compared with those used for therapeutic x-ray. The fact that acute effects are not observed clinically gives us a sense of security in using these doses. Certain questions should be raised:

1. Is it justifiable to assume that long range biologic effects of ionizing radiation will be innocuous if it is administered during early infancy?

2. Is there reason to suspect that recovery from fluoroscopic doses of x-ray is incomplete?

TABLE 1

Roentgen Procedure	Customary Roentgen Dose*
Fluoroscopy	10 to 20 r/min
Chest film	0.05 r
Other common films	1.2 r each
Dose to ovaries per film study of abdomen	0.2 r
IV pyelogram	7 to 8 r for series of 6 films
Barium contrast studies	10 to 20 r/min. for fluoroscopy and 1.2 r for each film
Dental film studies	1 to 15 r/film (average 5 r)
Diagnostic studies for congenital heart disease	140 r or more
Thymus treatment	75 to 350 r
Acne treatment	500 to 1000/treatment course

* See text for references.

3. If recovery is incomplete, what relationship is there between the medical use of roentgen rays and life in the atomic age?

In 1942, before the Hiroshima experience, Buschke and Parker[16] wrote of the possible hazards of repeated fluoroscopy of infants, and partially answered some of these questions. They described possible acute and genetic effects. Since the detonation of the first atomic bomb, interest in radiobiology has increased immensely. Recent attention has been directed to tolerance studies, cumulative effects, and late developments induced by ionizing rays. The remainder of this paper will be devoted to these current studies in an attempt to introduce to the clinician some of the observations made since Buschke and Parker published their paper.

Late Effects: 1. Genetic.—Muller's experiments[3, 21, 22] using the fruit fly imply that there is no tolerance range for the mutagenic effect, so that even the smallest exposure of the gonads to ionizing radiation produces an increase in the mutation rate. Because of the large number of animals necessary and because of the time required to follow them through many generations, it is difficult to repeat this work using mammals. Charles,[23] however, has demonstrated an increase in the mutation rate of the mouse. It is estimated that as little as 30 r[24] may be detrimental for the human testes or ovaries. Since there is no recovery, each exposure is additive to that previously administered to the patient.

Mutations produced by radiation are predominantly of a recessive Mendelian character. It would, therefore, require several generations before the anomalies conceived in our time would begin to make their appearance clinically. The number of individuals affected would be expected to increase progressively with the creation of each new generation provided that the abnormality produced was not lethal before the child-bearing age was attained. Because mutations caused by x-ray differ in no way from those occurring spontaneously, their direct relationship in the human would be difficult to establish. Only the mutation rate would change. It can then be realized why there is little expectation that the commission which is following the medical status of the people of Hiroshima and Nagasaki will uncover any convincing information about human genetics and its relation to atomic energy.

The ionizing radiation, the effects of which are stored in the gonads, reaches these organs either by their inclusion in the radiation field (intravenous pyelograms, G.I. studies, intubations) or by the scatter or deflection of rays directed primarily at some other area of the body. In fluoroscoping the chest, for example, the table, screen and bones

of the patient alter the course of the radiation so that some of it is directed to all parts of the patient's body. Martin[6] has determined that the ovaries receive 0.2 r each time a film of the abdomen is made. While this amount is small, it may nevertheless be genetically influential and additive throughout the patient's life. The practice of pediatrics is especially apt to contribute to this possible detriment because almost all patients are probable parents of the future, and the recurrent x-ray exposure they sustain may compromise the "hereditary dowry" they will bestow on their progeny. Even if Muller's data are eventually proved to be inapplicable to humans, it would seem best for those ordering roentgen examinations and therapy at present to assume that the conclusions experimentally derived from animals are valid for man.

In addition to the appearance of congenital anomalies, defects of the germ plasm may be manifested by an increase in abortions, premature births, or infertility. Boche et al.[25] have done some preliminary work which shows infertility of the mouse when it is mated 120 and 180 days after irradiation.

2. Shortened Life Span (unrelated to carcinogenesis).—Premature aging of animals is a recently described biologic event which is a consequence of chronic radiation or exposure to a single large dose of x-ray. It has not been recorded as a result of partial body radiation. There is wasting of the body, early greying of the hair, and easy fatigability.[26, 27] Death takes place at an earlier age than usual, for a cause that is often not determinable. In general it can be said that the animals appear senile prematurely. If such changes can occur as a sequel of partial body radiation, one would wonder if the amount of x-ray absorbed by the chest early in life during the diagnostic work-up of the congenitally defective heart would result in premature aging of the heart, thus impairing function already suboptimal.

3. Tumor Production.—Carcinogenesis is in a sense a detective story in which several good clues have been uncovered. It has been suggested by Henshaw[4] that cancer is an aberrant cellular differentiation, "differentiation at a tangent or beyond normal limits." This may be initiated by the introduction into the cell of some external factor such as a virus, or a physical or chemical agent. The effect of one external agent when combined with another may be synergistic or antagonistic.[28] X-rays presented intermittently throughout life may be completely or partially cumulative.[3, 5, 10, 23, 29–31] They may act by altering a special substance within the cell: either the gene itself, or a substance extragenic which influences the reproduction or growth of the cell. This change may not be reversible. The cell can then be considered to have been transformed into a pre-neoplastic state. Subsequently, if the host has the hereditary tendency, with the passage of time homeostatic shifts that occur with aging, infections, or in response to the environment will produce another alteration in the differentiation of the cell which may then cause the development of clinically detectable cancer. Thus cancer is thought not to be a sudden change in the differentiation of the cell. It seems as if it stems from the influence of many agents, one of which is ionizing radiation, which presumably primes the cell of the susceptible host for the next step in the neoplastic process.

There is evidence both from the laboratory and from human statistics to substantiate this concept. Some of the facts known will be cited.

Adult mice of a certain pure bred strain, as a result of total body exposure, develop a very high incidence of leukemia as compared with nonirradiated controls. Strangely enough this susceptibility is not present if the upper or lower halves of their bodies are shielded during the radiation.[32] Mice are extremely susceptible to x-ray-induced cancer

including leukemia. Results obtained through experimental with this species must be regarded for this reason with some suspicion in likening it to the human response.

However, there are now several reports which indicate that radiologists succumb to leukemia 8 to 10 times more frequently than do physicians who are not primarily engaged in this specialty.[33, 34] The possibility that this is a chance finding is only one in a billion. This fact is startling when it is considered that the radiologist receives low doses of soft radiation and that he may be partially shielded by his lead apron.

The Atomic Bomb Casualty Commission in studying the effects of radiation in the survivors of Nagasaki and Hiroshima have found what appears to be a real increase in the incidence of leukemia,[35] despite the fact that only five years have elapsed since the exposure. This is evidence that even a single sufficiently extensive exposure can induce leukemia in man.

Factors on which radiation-induced cancer depends are best revealed by animal experimentation. Although the conclusions are subject to some uncertainty when applied to man, they do serve to show which possibilities cannot be excluded.

Is x-ray-induced neoplasia more closely related to the total dose administered or to the dose rate (roentgen exposure/minute)? Mouse ovarian cancer seems to be a function of the total dose and develops after 25 to 50 r have been provided.[10, 31] On the other hand, the dose rate is the more influential factor in the roentgen ray induction of mouse lymphoma, lung cancer and mammary cancer.[10] In some instances, then, carcinogenesis is more closely related to the total dose, while in others it is more dependent on the dose rate.

Is total body exposure necessary to induce cancer by x-ray? Cancer of the lung of mice has been produced by exposing this organ to roentgen rays while the rest of the body was shielded by lead.[10] Patients treated with high doses of roentgen rays have developed cancer of the skin[36] or bone[37-39] although only small areas of their bodies were exposed. Therefore, total body irradiation was not necessary for the induction of neoplasia in these organ systems.

An important consideration for the pediatrician is the susceptibility of the infant to x-ray exposure. Is it greater or less than that exhibited by the adult? The experimental work on this problem has just begun. Kaplan[9] has revealed that pure bred mice, age two weeks to one month, are much more apt to develop leukemia than are older mice. The latent period between the exposure and the onset of the illness was shorter in the young animals. Lorenz[10] irradiated newborn mice, in which the spontaneous incidence of leukemia was low, with 400 r and showed that 25% developed the disease before they were seven months old. Even if his susceptibility is not greater than the adult's, the human infant's long life expectancy may make him a better candidate for the development of the late effects of ionizing rays.

After the late effects of a single partial body exposure of young animals to a low dose of x-ray has been defined, it will be desirable to learn if chronic infection, anemia, malnutrition, anoxia and other pre-existing subnormal states can increase or decrease the likelihood that the animal will develop these sequelae. Such knowledge would indicate whether the ill pediatric patient is more susceptible to the side effects under discussion. An ailing child is the one most apt to be subjected repeatedly to fluoroscopic examination.

Certain hormones can change the incidence of the delayed pathologic events of x-ray. The frequency of the induction of mouse lymphoma is decreased by testosterone[40] and cortisone[41] whereas it is increased in adrenalectomized animals[41] or those given estrogen.[42]

The effects of other biologic products and therapeutic agents have yet to be defined.

Why should we believe that man can show a latent period of years after seemingly innocuous injury produced by a physical agent? It may be that the physiologically altered cells so produced in him lose their pre-cancerous tendencies before neoplastic changes can occur. Treves and Pack[43] have described 22 patients who developed neoplastic skin changes at the site of a thermal burn following a long symptom-free period. Eight of these patients were less than 10 years of age at the time they sustained their injuries. The average latent period for them was 42 years, the maximum was 62 years, and the minimum was 14 years. Those patients who develop cancer of the skin or bone following roentgen therapy do so after a latent period ranging from a few years to several decades.

It is generally believed that doses of x-ray less than 50 r will have no clinically detectable acute effect in the human other than a slight transient reduction of lymphocytes and neutrophiles.[44] However, the acute effect may not be the limiting factor in the estimation of the tolerance dose. Stone[45] has said that it seems as if neither the skin nor the hemopoietic systems entirely recover from even minor damage caused by x-rays, while Furth's experiments[31] (increased incidence of ovarian neoplasia in mice following single whole body doses of only 25 to 50 r) lead him to believe that the ovary should be included in Stone's statement. Brues has written that ". . . malignant disease and hereditary changes, characterizing as they do the smaller radiation doses, are in the final analysis the known factors that determine safe or acceptable levels of exposure, and at the same time are the most difficult of experimental understanding. . . . It may be concluded that clear instances of radiation carcinogenesis by dosages lower than 1000 human roentgen equivalents are lacking, although the possibility of such effects resulting from lower dosages, either as statistical accidents or due to individual susceptibility, is not ruled out."[5]

It would appear, then, from the available data, that there is more than a suspicion that man, especially during the early years of his life, can acquire from therapeutic and diagnostic roentgen procedures some of the ingredients of carcinogenesis. It must be kept in mind that neoplasia induced by x-ray would duplicate that occurring spontaneously, and that it would appear at the usual manifestation age of the naturally occurring disease. Therefore direct implication of x-ray in its genesis could only be accomplished by recognizing an over-all increase in the incidence of cancer in exposed individuals.

4. Other Effects.—Bennett et al.[46] have recently described the appearance in irradiated rats (supralethal doses given while the animals were temporarily anoxic) of nephrosclerosis with hypertension and a blood dyscrasia which seemed to be of the hypersplenic type. This species does not ordinarily develop these pathologic conditions. The rats showed other degenerative changes (indicating early senility) and diminished life span. The authors felt that the brief period of anoxia was not contributory to these developments. The suggestion is that the medical cycle of the animals' lives was concentrated. Therefore, a disease which cannot show itself because its manifestation age lies beyond the animal's life expectancy may be able to do so after x-ray exposure.

X-ray Therapy: Roentgen therapy for the pediatric patient with malignant disease is, of course, completely justifiable when other treatment offers a less satisfactory prognosis. The possibility of undesirable side effects years hence should not be overlooked. It has been reported[47] that a 14 year old girl who had a congenital embryoma (left side) removed at 19 months of age developed scoliosis and shortening of the left leg, presumably a growth arrest secondary to postoperative x-ray therapy. Similar bone growth changes have been reported in three children who received intensive irradiation for treatment of cancer.[48] Time may reveal the presence of other late effects.

The case against roentgen therapy for benign disease for which satisfactory alternative treatment exists is easier to formulate. The irradiation of facial hemangiomata when improperly shielded has been postulated as a cause for inhibition of tooth bud growth.[49] Giant cell tumors of bone have been successfully treated with x-ray only to have malignancy appear in their places years later.[37] Malignancy has also followed roentgen therapy for bone tuberculosis.[37] The elective use of x-irradiation by the physician for the relief of such ailments as enlargement of the thymus, the cough of virus pneumonia, acne and various conditions of the skin should not be considered to be unquestionably safe until more is known about the pathogenesis of x-ray-induced diseases.

The Atomic Age and X-rays: X-irradiation is atomic energy. By its overuse in pediatrics a child's tolerance for this physical agent may be dissipated. The child of today faces a life of repeated exposures to atomic energy. Even if he does not become an aviator exposed to the elevated cosmic ray dosage of high altitudes, or a worker in industry where x-rays or radioactive power are employed, or a hospital or laboratory worker exposed to x-ray machine emanations and radioisotopes, he is still apt to be a soldier or civilian involved in an area of radioisotope contamination, or a patient who needs diagnostic fluoroscopy or x-ray therapy. With the possibility that atomic energy will be so frequently encountered in the life of the immediate future, it would seem advisable to limit elective procedures as much as feasible.

The pediatrician should be aware of these potentialities. Perhaps it would be wise for him to advise only those roentgen procedures which apply to problems that can be solved by no other technic. This would preclude the use of the fluoroscope for the routine examination of the chest. Studies which will have to be repeated by a more experienced fluoroscopist, as may occur in the diagnosis of congenital heart disease, should not be attempted. In general, when a film can be expected to give reasonably adequate information, it should be obtained in preference to fluoroscopy.

Poppel and his co-workers[17] have recommended that roentgen exposure diaries be kept for all patients. This would enable the physician in the community, in the army, and in industry to be conscious of the accumulation of x-rays absorbed by the patient. When the individual seeks a new doctor, the physician chosen would possess the estimated roentgen dose to date and could be guided accordingly in his approach to the case. A comparison of diaries might aid in the implication of x-ray in the development of certain diseases.

Summary

Life in the atomic era has brought with it increased exposure to ionizing radiation. Radiobiology is concerned with the study of the effects of this physical agent. The clinical application of the facts derived experimentally may apply not only to atomic bomb catastrophes, but also to exposures to x-rays in daily medical practice.

Ionizing radiation may alter a key physiologic process thus producing an aberrant cellular differentiation. An undetectable acute change may set the stage for the appearance after a long latent period of (a) congenital anomalies or infertility; (b) carcinogenesis; (c) premature aging and degenerative changes.

Minimal dose levels for producing these changes in humans is not known. However, experimental work to date indicates that the young recipient of x-rays is more apt to develop late sequelae than is the adult. In addition, his longer life span makes him a more likely subject for such changes. Because of unavoidable exposure to irradiation in industry, medicine and warfare, it is suggested that elective pediatric roentgen procedures be limited as much as possible. Roentgen exposure diaries for patients are recommended.

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University of Rochester School of Medicine and Dentistry

NEWS AND ANNOUNCEMENTS

Announcement is made of a 2 Week Postgraduate Course in General Pediatrics, Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston, under the auspices of the Harvard Medical School, June 8 through June 20, 1953. Clinics providing a broad review of pediatrics emphasizing the new advances will be given daily from 9:00 A.M. to 4:30 P.M. by selected authorities from the Pediatric and Specialty Services of the Massachusetts General Hospital and the Children's Medical Center, Boston.

For further information write: Assistant Dean, Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston.

* * *

A fellowship in pediatric cardiology at the University of Utah is being offered for one year starting July 1, 1953. Both clinical and laboratory training in congenital and rheumatic heart disease will be given and will include cardiac catheterization and angiocardiograph.

Applicants will be considered on the basis of former training and military status. The annual stipend will be $3000 for an unmarried fellow and $3600 for a married fellow. Applicants should write to: University of Utah College of Medicine, Department of Pediatrics, Salt Lake General Hospital, Salt Lake City.

* * *

The Cook County Graduate School of Medicine announces a 2 week intensive course on "The Diagnosis and Treatment of Congenital and of Rheumatic Heart Disease in Infants and Children," from May 18 to May 30, 1953. For a circular giving full information, write to: Registrar, Cook County Graduate School of Medicine, 707 S. Wood St., Chicago.

* * *

Latest step in the steady growth of Endo Products Inc., Richmond Hill, N.Y., pharmaceutical manufacturers, is the opening of a new West Coast office and warehouse in Los Angeles according to an announcement by Joseph Ushkow, president of the firm. Officially opened on Feb. 1, the West Coast branch is housed in a new, thoroughly modern, one-story structure located at 11400 W. Olympic Blvd. (corner Purdue Ave.). All West Coast sales and warehousing operations are directed from this building by H. L. Wellington, West Coast Manager.

* * *

The following diplomates have been certified by the American Board of Pediatrics, Inc.:

Boston—Dec. 5, 6 and 7, 1952

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BOOK REVIEWS

MEDICAL INSPECTION OF SCHOOL CHILDREN, Edgar Henry Wilkins, M.B., B.Ch. (Dublin), D.P.H. (London), Baltimore, Williams & Wilkins Company, 1952, $4.00, 224 pp.

Edgar Henry Wilkins, for many years a school medical officer in New Zealand and in Birmingham, England, died in 1946 with the manuscript for this book partly in draft stage and partly with little more than notes or an expression of intensions. It was completed by the School Health Service Group of the Society of Medical Officers of Health with Dr. Wilkin's daughter, Mrs. Ernst Kaiser, as literary executrix in charge of the work.

The book does not limit itself, as its title would indicate, to medical inspection, but rather to the technical duties of the school physician under the present system of social medicine in England, of discussion of the position of the school physician in a comprehensive school health program. While much of the underlying philosophy concerning the health of the school child is sound, its application under a system radically different from that of the United States is confusing and impractical in our plan of medical practice, and in places takes on the hue of propaganda rather than that of scientific medicine.

Diagnosis is discussed in a curious manner. For example, in considering anemia, the use of hemoglobinometer is not advised since it would greatly prolong the time spent on each case, and moreover it requires skill and experience. After admitting that without it, anemia cannot be distinguished from "poor general health" it is suggested that "the administration of ferrous sulphate supported by adequate protein, Vitamin B Complex and C may remedy symptoms and improve the colour." This is not an isolated instance of a technic in school health the rationale of which escapes this reviewer.

Since treatment as such is not a part of the duty of our school physicians, its inclusion in the book is startling. A consideration of these sections leaves one with mixed feeelings: first, a sense of satisfaction that the American system of delegating all treatment to the private physician and other remedial agencies is much to be preferred for the well being of the school child; second, a fear that the novitiate in school health might, after reading this book, attempt therapy as outlined, with possible unfortunate results both to the school child and to his own reputation.

There is little to recommend in this book except to the collector of bibliographic curiosa.

VACCINATION PAR LE BCG, R. Mande and A. Huët, Paris, International Children's Centre, 1951.

Under this title, the International Center of Childhood describes in detail the study made by the central BCG station of Paris on the results of various tuberculin tests applied before and after vaccination with different brands of BCG vaccine. The study began in 1948 and is presented under 6 headings.

The first chapter deals with various tuberculin tests: Mantoux skin test, cuti reaction of von Pirquet and the Finnish reaction, including the various concentrations of tuberculin. This is a good discussion on the various methods of tuberculin testing.

Chapter 2 deals with the methods of vaccination and the evolution of the local reaction. Three methods of vaccination are studied: (1) intradermal (Wallgren); (2) cutaneous scarification (Negre and Bretey); (3) multiple punctures (Rosenthal).

Chapter 3 is concerned with the postvaccinial allergy encountered in the 3 methods of vaccination and the problem of an added infection with tuberculosis.

The fourth chapter discusses the complications arising after BCG vaccination, that is, general and local reactions with the different methods of vaccination and different brands of vaccine.

BCG vaccine vitality and the etiology of variations in this vitality is the subject considered in chapter 5.

The sixth chapter completes the third one (a study of the vaccine of the Pasteur Institute of

Paris) in that it adds information on 2 additional vaccines, namely: the vaccine of the Serum Institute of Copenhagen and the Swedish vaccine (Goleborg).

This, in the reviewer's opinion, is the best book ever presented on the subject of BCG vaccination. It deals with all the available information regarding the technic of vaccination: the reader will suffer no loss of time with historical facts easily found elsewhere.

The groups of vaccinated patients are large enough to draw conclusions on the effectiveness of BCG vaccination; a future publication will deal with these conclusions.

ÉTUDES NÉO-NATALES, Paris, International Children's Center; subscriptions arranged through Lange, Maxwell & Springer, London, £/18/6) per year.

A new pediatric journal has been started entitled *Études Néo-Natales* (Neo-Natal Studies), a quarterly review published in French and English under sponsorship of the International Children's Center in Paris. The first volume began in February 1952.

The editorial board of 14 includes Drs. Edith Potter, Henry Barnett and Clement A. Smith as American representatives. The other editors are names familiar to everyone doing research upon the newborn. The editorial policy is to publish review articles by pediatricians, obstetricians, pathologists, physiologists and authorities in every other field which can contribute to knowledge of human adjustment from intra- to extrauterine life. The first numbers of this review indicate that the policy will be followed with considerable success. *Neo-Natal Studies* is a welcome addition to pediatric literature.

VISCERAL INNERVATION AND ITS RELATION TO PERSONALITY, Albert Kuntz, Ph.D., M.D., Springfield, Ill., Charles C Thomas, Publisher, 1951, $4.50.

Written by a well known neuroanatomist this book may serve people in many disciplines. It is a concise account of the anatomy and physiology of nerves which supply the visceral organs, demonstrating the influence of the functional state of the viscera on human behavior and personality. Child psychiatrists will find this a valuable basic book, but the busy pediatrician too will benefit from this small volume in learning (or re-learning) anatomy and physiology of the nervous system. If neurology can ever be made easy reading, this monograph approaches such a goal in a very satisfactory manner.

DIAGNOSTICHE UND THERAPEUTISCHE TECHNIK BEIM KINDE (DIAGNOSTIC AND THERAPEUTIC TECHNIC IN PEDIATRICS), Kurt Nitsch, Stuttgart, Georg Thieme Verlag, 1951, DM 14.70, 168 pp., 26 illustrations.

Outlines on technical procedures that are presented in a small volume and not scattered in a clinical textbook are of great value for residents and interns. Not every otherwise capable intern is technically minded. He should be given the opportunity to think over procedures instead of imitating mistakes that are traditionally handed down by generations of residents. The author's teacher was Kleinschmidt, a leading German pediatrician, whose school guarantees wise selection and avoids polypragmasy. His own experiences in the large Children's Hospital of Bad Orb enabled him to present in a concise form and with the cooperation of his wife, who made the instructive drawings, the following main chapters: general methods such as immunizations, artificial respiration, desensitization; physical therapy; methods related to blood and blood vessels, from subcutaneous injections to exchange transfusions; procedures applied to upper respiratory passages; pulmonary airways, including intubation and pneumothorax; intestinal tract, urogenital organs, liquor and skin.

The author emphasizes in his foreword the necessity of this outline, since the last German textbook on pediatric technic was published by Behrendt in 1933. However, it is not justified to dismiss this older textbook as an outdated publication. The classical methods (spinal puncture, intubation) are even more instructive in the outline of Behrendt. This new book can be highly recommended to those who read German, in spite of differences in the German and American methods (e.g., intravenous drip infusion is not much used in Germany).

PATHOLOGY OF FETUS AND THE NEWBORN, Edith L. Potter, M.D., Chicago, Yearbook Publishers, Inc., 1952, $19.

This is the first adequate book on the subject in a field where there has long been a serious need. In no other single reference in the English literature can one find such a complete and concise presentation of the pathology, pathogenesis, pathophysiology, clinical relationships, and the public health aspects of mortality in the fetus and the newborn.

Dr. Potter is Associate Professor of Pathology in the Department of Obstetrics and Gynecology of the University of Chicago; she is pathologist for the Lying-In Hospital and chief pathologist for the Chicago Department of Health. In view of her associations, it seems natural that she should approach this subject in a manner distinct from the approach of either a pediatrician or the usual pathologist. The early part of the book is organized about the chronologic development of the fetus from various phases of antenatal growth through problems of the full term infant. The later portion is devoted to diseases of the various systems.

The work must have been a labor of love. This feeling is indirectly expressed in one sentence of the Preface, "Only if this work ultimately helps save the lives of infants who might otherwise die, will it have been worth the effort expended in its production." This reviewer considers that Dr. Potter should feel well rewarded for her tremendous effort by the good effect her book is sure to have.

The material is based upon data accumulated over a period of 18 years. During this time, 6000 autopsies were performed on infants and fetuses dying in the Chicago Lying-In Hospital. In addition tissues from over 3000 additional autopsies were sent to Dr. Potter by pathologists from the Chicago Department of Health. Added to this, Dr. Potter reviewed over 10,000 protocols of autopsies on live born infants dying under one year of age in other hospitals in Chicago. Her personal experience is therefore impressive.

The next edition could be improved by inclusion of more references to published literature, more recent information on such items as the role of mucoviscidosis in cystic fibrosis of the pancreas, the pathogenesis of Hirschsprung's disease and the use of currently accepted classifications of bacteria.

Dr. Potter has a style which is clear and easy to read. The book is thoroughly illustrated with excellent photographs. The paper is excellent, and the binding is sturdy.

This book represents a milestone. It is of great importance to obstetricians, pediatricians, pathologists, and to public health officials interested in neonatal death.